

Synthesis of Both Enantiomers of Phoracantholide I, a Defensive Secretion
of the Eucarypt Longicorn, Employing Asymmetric Reduction with
Immobilized Baker's Yeast

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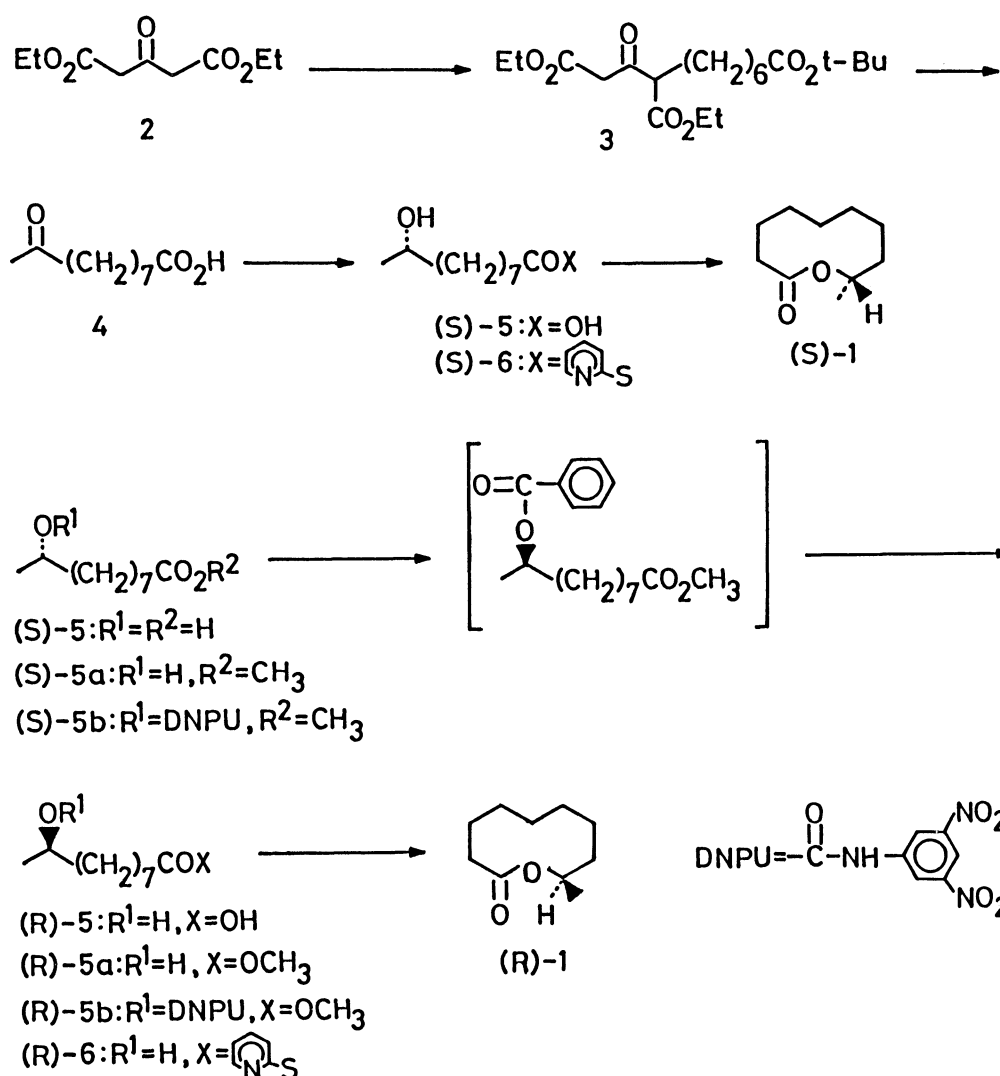
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Highly enantiomerically pure (R)- and (S)-phoracantholide I were synthesized in relatively short steps starting from diethyl 3-oxoglutarate by means of an asymmetric reduction of the intermediate keto acid with immobilized baker's yeast. The asymmetric reduction with the immobilized baker's yeast gave greater facilities compared with the analogous reaction with free baker's yeast.

Since phoracantholide I (1), possessing a ten-membered lactone ring, had been isolated as a defensive secretion from the metasternal gland of the eucarypt longicorn, *Phoracantha synonyma*,¹⁾ several synthetic methods were reported for racemic 1.²⁾ The first synthesis of optically active 1 has recently been achieved by Kitahara et al. and the (R)-enantiomer announced as the natural form of a defensive secretion of the insect.³⁾ However, the method required multiple steps and the optical purity of synthesized enantiomers based on their GLC analyses with a chiral stationary phase was somewhat low, 89% e.e. We report herein a facile and short-step synthesis of highly enantiomerically pure (R)- and (S)-1 from diethyl 3-oxoglutarate (2). The key feature of our approach is that the chiral center in optically active 1 comes from the asymmetric reduction of the keto acid 4, which was easily prepared from 2, employing baker's yeast immobilized in λ -carrageenan beads.

First, diethyl 3-oxoglutarate (2) was alkylated regioselectively with t-butyl 7-bromoheptanoate and $Mg(OEt)_2$ to give the monoalkylated 3-oxoglutarate 3,⁴⁾ which was converted by a decarboxylative hydrolysis to the keto acid 4,⁴⁾ mp 41-42 °C,

with a 78% yield from 2. Compound 4 was then subjected to an asymmetric reduction employing the baker's yeast immobilized in λ -carrageenan^{5,6}) to give an optically active alcohol (S)-5,⁴) [α]_D²²+8.14° (c 0.14, CHCl₃), which showed an optical purity of 96% e.e.⁷) Finally, (S)-5 was lactonized via the corresponding pyridine-thiol ester (S)-6 in the presence of AgClO₄ to give (S)-1^{8,9}) with a 44% yield, [α]_D²²+38.38° (c 0.06, CHCl₃)[lit.³[α]_D²²+34.8° (c 0.68, CHCl₃)]. For the synthesis of (R)-1, the methyl ester (S)-5a was converted via a Mitsunobu inversion to (R)-5,⁴) [α]_D²³-8.13° (c 0.11, CHCl₃), with an optical purity of about 95% e.e.⁷) Lactonization of (R)-5, as described above, gave (R)-1,^{8,9}) [α]_D²²-37.4° (c 0.02, CHCl₃)[lit.³[α]_D²²-35.1° (c 1.15, CHCl₃)]. Thus highly enantiomerically pure (R)- and (S)-1 were synthesized with seven- and four steps from 2, respectively.



Scheme 1. Synthesis of (S)- and (R)-1.

Table 1. Repeated Use of Immobilized Baker's Yeast in
the Asymmetric Reduction of the Keto Acid 4

Recycle number	Yield %	Optical purity of (S)- <u>5</u> % e.e.	Specific rotation of (S)- <u>5</u> $[\alpha]_D^{22}/^\circ(c, \text{CHCl}_3)$
1	12	95.5	-
2	23	96	+8.13 (c 0.23)
3	36	96	+8.13 (c 0.32)
4	35	96	+8.13 (c 0.33)
5	43	96	+8.14 (c 0.41)
6	40	96	+8.14 (c 0.35)
7	18	96	+8.13 (c 0.12)
8	6	95.5	+8.13 (c 0.036)
1a)	36	92	+8.10 (c 0.32)

a) Use of free baker's yeast (40 g).

As shown in Table 1 the reuse of the immobilized baker's yeast catalyst was tested. Although the first use of the baker's yeast catalyst gave a low yield of (S)-5, 12%, a maximum yield of 43% was obtained after 5th use and after 8th use the catalyst still maintained the activity showing a 6% yield. The activity of the immobilized baker's yeast appeared to be comparable with that of free baker's yeast.

It is important to note that (1) the present baker's yeast catalyst immobilized in κ -carrageenan beads was able to be stored in an aqueous solution of KCl for six months at 0-5 °C, (2) the catalyst was reusable 8 (or more) times during the period, (3) the optical purity of the product (S)-5 was almost constant throughout all of the use of the catalyst, and (4) the catalyst was able to be recovered and separated easily from the reaction mixture by simple filtration.

Further applications of the immobilized baker's yeast to synthetic chemistries, including the comparison with free baker's yeast (e.g. yield, optical purity, and stereochemistry of the product and activity of the catalysts), will be investigated.

References

- 1) B. P. Moore and W. V. Brown, *Aust. J. Chem.*, 29, 1365 (1976).
- 2) H. Gerlach, P. Kunzler, and K. Oertle, *Helv. Chim. Acta*, 61, 1226 (1978); T. Takahashi, S. Hashiguchi, K. Kasuga, and J. Tsuji, *J. Am. Chem. Soc.*, 100, 7424 (1978); T. Wakamatsu, K. Akasaka, and Y. Ban, *J. Org. Chem.*, 44, 2008 (1979); E. Vedejs, and D. W. Powell, *J. Am. Chem. Soc.*, 104, 2046 (1982); N. Ono, H. Miyake, and A. Kaji, *J. Org. Chem.*, 49, 4997 (1984).
- 3) T. Kitahara, K. Koseki, and K. Mori, *Agric. Biol. Chem.*, 47, 389 (1983).
- 4) Compound 3, 4, and (R)- and (S)-5 were fully characterized on the basis of their spectral data and elemental analyses.
- 5) A procedure for the immobilized baker's yeast reduction is as follows: A mixture of D-glucose (40 g) and baker's yeast (Oriental Yeast Co., Ltd., Tokyo, 40 g) immobilized in λ -carrageenan beads in a 2% aqueous solution of KCl (1000 ml) was shaken for 6 h at 30-35 °C, and to the fermenting mixture D-glucose (40 g) and the potassium salt derived from 4 (1 g) were added. After the mixture had been shaken for 48 h at 35 °C, the baker's yeast and solution were separated by filtration. The solution was extracted with ether and the ethereal solution was worked up. The product (S)-5 was purified by a combination of column chromatography and preparative TLC on silica gel.
- 6) T. Tosa, T. Sato, T. Mori, K. Yamamoto, I. Takata, Y. Nishida, and I. Chibata, *Biotechnol. Bioeng.*, 21, 1697 (1979).
- 7) The optical purities of (R)- and (S)-5 were determined by the HPLC analyses of the corresponding 3,5-dinitrophenylurethane (DNPU) derivatives, (R)- and (S)-5b, employing a chiral stationary phase. HPLC was carried out Gasukuro Kogyo model 576 liquid chromatograph equipped with a UV detector. A Sumipax OA 2100 4 mm x 25 cm column (Sumitomo Chemical Co., Ltd., Osaka) was used with hexane-1,2-dichloroethane-ethanol (100:20:1) as solvent.
- 8) Compounds (R)- and (S)-1 were fully characterized by comparing their spectral data with those reported.³⁾
- 9) The optical purities of (R)- and (S)-1 would be at least 95% e.e., because it was assumed that no apparent racemization at the chiral center of (R)- and (S)-5 had occurred during their lactonization.

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