Tetrahedron Letters,Vol.26,No.6,pp 771-774,1985
Printed in Great Britain

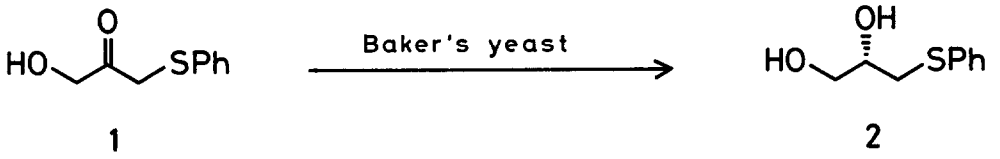
0040-4039/85 $3.00 + .00

OPTICALLY PURE (S)-3-PHENYLTHIO-1,2-PROPANEDIOL: SYNTHESIS BY THE YEAST REDUCTION AND USE AS A PRECURSOR OF BOTH ENANTIOMERS OF SECONDARY ALCOHOLS

Tamotsu Fujisawa,* Toshiyuki Itoh, Mikio Nakai, and Toshio Sato
Chemistry Department of Resources, Mie University, Tsu, Mie 514, Japan

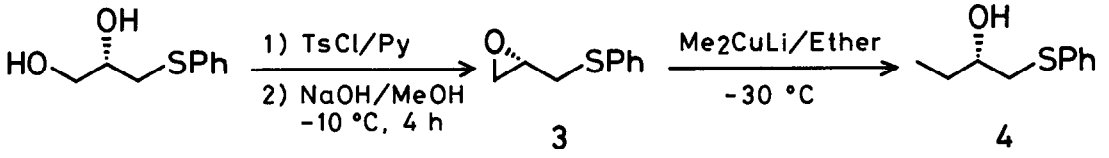
Summary: *Optically pure (S)-3-phenylthio-1,2-propanediol was obtained by the enantioselective reduction of 1-hydroxy-3-phenylthio-2-propanone with the Baker's yeast, and was found to be a convenient precursor for both enantiomers of secondary alcohols, which was demonstrated in the synthesis of both enantiomeric forms of 5-hexadecanolide via phenyl (S)-glycidyl sulfide as the key intermediate.*

Recent efforts directed toward the synthesis of complex natural products have pointed out the need for a variety of versatile chiral synthetic intermediates so called "chiral building blocks".[1] Easily available ones are prepared from chiral materials produced in nature including carbohydrates, amino acids, hydroxy acids, terpenes and so on.[2] It is frequently noted, however, that these compounds are far from being satisfactory as the chiral building block, since the major limitation arising from the fact that most of these compounds are available in only one enantiomeric form in nature. Consequently a new chiral building block giving both two enantiomers is expected. Especially to obtain both enantiomers of secondary alcohol, we noted optically pure phenyl glycidyl sulfide (3).[3] The reason is that the subsequent reaction with variety of nucleophiles gives optically pure β-hydroxy sulfide, which can be transformed again into new optically active epoxides with retention of the chiral ceter. Further the subsequent nucleophilic ring-opening of the newly formed epoxide can lead to a wide variety of optically active secondary alcohol derivatives. It should be expected that both enantiomeric forms of secondary alcohols may be obtained by the exchange of the order of two nucleophilic ring-opening reaction of the optically active glycidyl sulfide 3. We wish to report here the simple preparation of optically pure (*S*)-3-phenylthio-1,2-propanediol (2) by the enantioselective reduction of the corresponding 1-hydroxy-3-phenylthio-2-propanone (1)[4] with the Baker's yeast *(Saccharomyces Cerevisiae)* and the successful results of synthesis of both enantiomeric forms of insect pheromone (*R*)-(+)- and (*S*)-(-)-δ-*n*-hexadecanolides[5] *via* (*S*)-glycidyl sulfide 3.



1 2

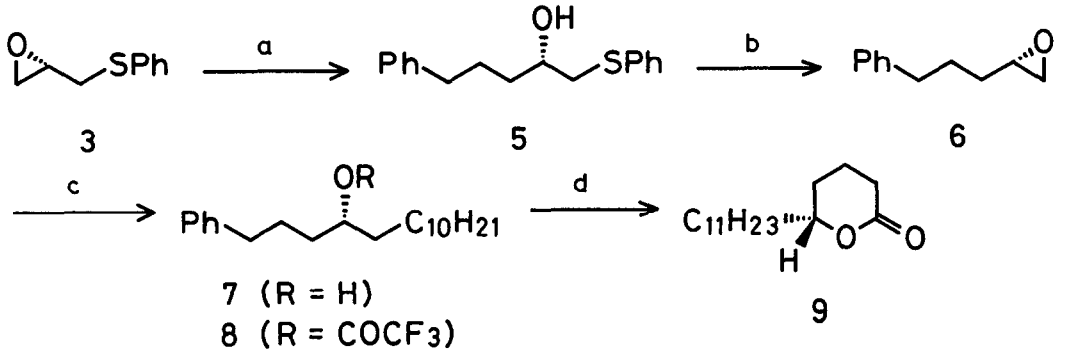
To a fermented suspension of the Baker's yeast and sucrose was added an ethanol solution of 1, and the reaction mixture was stirred for 24 h at room temperature. After the usual workup, the corresponding optically active glycol 2 was obtained in 90% yield. To confirm the absolute configuration and optical yield, selective tosylation of the primary hydroxy group in the glycol 2 followed by an alkaline treatment gave the glycidyl sulfide 3, which then reacted with lithium dimethylcuprate to give 1-phenylthio-2-butanol (4).[6] By comparison with the specific rotation data of pure 4, glycol 2 obtained by the fermentation with the Baker's yeast should be 78% ee.[7] After recrystallization from benzene, however, optically pure glycol 2 with *S* configuration was obtained in 63% yield.[8]



3 4

Since this glycidyl sulfide 3[9] is an asymmetric three carbon molecule, it may be suitable for the precursor of both enantiomers of secondary alcohols. To clarify the utility of the present compound, the synthesis of both enantiomeric forms of δ-hexadecanolide found in the mandibular glands of the oriental hornet, a kind of queen substance, was tried. The pheromone with *R* configuration was first synthesized. Thus, copper(I) catalyzed regioselective ring-opening of 3 with phenethyl Grignard reagent[10] gave β-hydroxy sulfide (5) in 90% yield; $[\alpha]_D^{23}$ +19.5° (c 1.054, $CHCl_3$). Treatment of 5 with trimethyloxonium fluoroborate (1.8 equiv.) and then exposure to aq. NaOH solution (2.5 M)[11] afforded the epoxide 6 in 80% yield; bp 140 °C/26 Torr (Kugelrohr), $[\alpha]_D^{23}$ -9.46° (c 1.036, $CHCl_3$). Then nucleophilic addition of 6 with decyl Grignard reagent in the presence of copper(I) iodide catalyst (20 mol%) gave the chiral alcohol 7 in a yield of 83%; $[\alpha]_D^{23}$ -2.10° (c 0.942, $CHCl_3$). After protection of the hydroxy group in 7 with trifluoroacetyl function (81%), ozonolysis of benzene ring in the trifluoroacetate 8 on silica gel,[12] followed by hydrolysis and subsequent lactonization afforded (*R*)-(+)-δ-*n*-hexadecanolide (9) in a yield of 49%; mp 39 °C, bp 190 °C/0.2 Torr (Kugelrohr), $[\alpha]_D^{23}$ +40.8° (c 0.760, THF); lit.[5d] $[\alpha]_D^{25}$ +39.97°.

On the other hand, the synthesis of the antipode of the pheromone was also achieved using two kind of Grignard reactions. Phenyl (*S*)-glycidyl sulfide (3) was converted into β-hydroxy sulfide (10), $[\alpha]_D^{23}$ +22.6° (c 1.254, $CHCl_3$), by copper(I) catalyzed reaction with decyl Grignard reagent in 88% yield. The

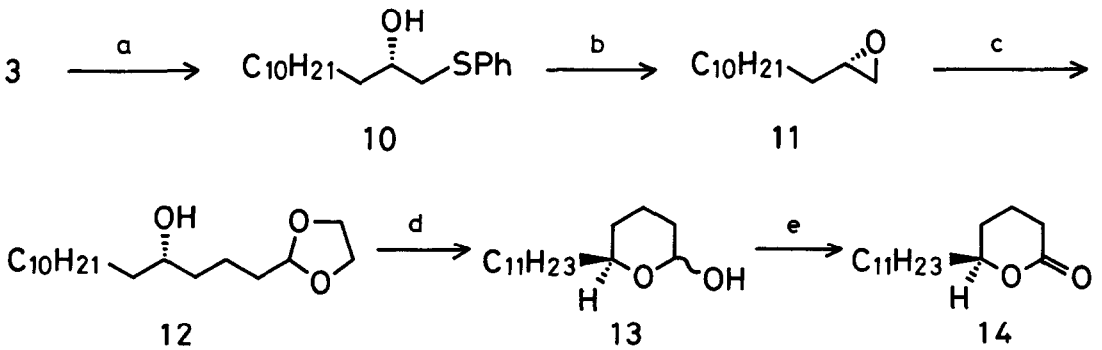


a: Ph⟋⟍MgBr (1.5 equiv.), CuI (20 mol%), THF-Me_2S (20:1), -30 °C. b: $Me_3O^+BF_4^-$ (1.8 equiv.) then treated with 2.5 M NaOH at rt. c: $C_{10}H_{21}MgBr$ (1.7 equiv.), CuI (20 mol%), THF-Me_2S (10:1), -20 °C, 7 → 8; $(CF_3CO)_2O$/Py. d: O_3/SiO_2, -78 °C, 12 h → $NaHCO_3$/THF-H_2O PH 8.3 → 2N HCl PH 3.5 → in $CHCl_3$ on standing rt 12 h.

same treatment of 10 as mentioned above gave the epoxide 11 (83%); bp 125 °C/0.15 Torr (Kugelrohr), $[\alpha]_D^{23}$ -12.1° (c 1.372, THF). Ring-opening reaction of 11 with the cuprate derivative prepared from 3,3-ethylenedioxypropylmagnesium bromide gave the chiral alcohol 12 (86%); $[\alpha]_D^{23}$ -1.35° (c 1.036, $CHCl_3$). Acid catalyzed hydrolysis of 12 at room temperature afforded the lactol 13 (81%), which was finally oxidized with pyridinium chlorochromate to give (*S*)-(-)-δ-*n*-hexadecanolide (14) in 88% yield by purification of silica-gel TLC and bulb-to-bulb distilation (180 °C/0.2 Torr); mp 39 °C; $[\alpha]_D^{23}$ -43.0° (c 0.744, THF), lit.[5d] $[\alpha]_D$ -39.2°.

Thus we could show that the enantioselective reduction using the Baker's yeast to afford optically pure (*S*)-3-phenylthio-1,2-propanediol, which easily converted into phenyl (*S*)-glycidyl sulfide (3) of the useful chiral building block for the synthesis of both enantiomers of secondary alcohol derivatives. It should be expected that this chiral building block could become a useful precursor for construction of optically active natural products.

Acknowledgment: The present work was partially supported by a Grant-in-Aid for



a: $C_{10}H_{21}MgBr$ (1.5 equiv.), CuI (20 mol%), THF-Me_2S (20:1), -30 °C. b: $Me_3O^+BF_4^-$ (1.8 equiv.), 2.5 M NaOH. c: [O⟋⟍O]$_2$CuMgBr (1.5 equiv.), THF, -30 °C. d: 10% H_2SO_4:acetone = 1:1, rt. e: PCC (2.0 equiv.) in CH_2Cl_2, rt.

Scientific Research from the Ministry of Education, Science and Culture in Japan, and the Naito Foundation.

References

1. D. Seebach and E. Hungerbühler, "Modern Synthetic Methods 1980," R. Scheffold Ed., Salle and Sauerländer-Verlag, Frankfurt and Aarau, 1980.
2. For example; S. Hanessian, "Total Synthesis of Natural Products: The 'Chiron' Approach," Pergamon Press, Oxford, 1983; K. Mori in "The Total Synthesis of Natural Products," Vol. 4, p. 1, J. Apsimon Ed., John Wiley & Sons, New York, 1981.
3. For the reactions of the racemic 3; N. Hamanaka, S. Hashimoto, and M. Hayashi, *Eur. Pat. Appl.*, Ep 44711 (1982), *Chem. Abstr.*, 97, 109778p (1982); H. Mildenberger, B. Sachse, and T. Maier, *Ger. Offen.*, 2908378 (1980), *Chem. Abstr.*, 94, 121542c (1981); E. R. Freiter, A. B. Abdallah, and S. J. Strycker, *J. Med. Chem.*, 16, 510 (1973); T. Fujisawa and M. Kakutani, *J. Polym. Sci., Polym. Lett. Ed.*, 12, 557 (1974); H. Sugimura and H. Takei, *Chem. Lett.*, 1505 (1984).
4. 1-Hydroxy-3-phenylthio-2-propanone (1); A solution of benzenethiol (20 ml) and triethylamine (50 ml) in DMF (20 ml) was added at 0 °C to a solution of dichloroacetone (20 mmol) and sodium acetate (24.5 mmol) in DMF (20 ml), and then stirred at room temperature for 1 h. 1-Acetoxy-3-phenylthio-2-propanone was obtained in 54% yield after silica-gel column chromatography. The acetate was hydrolyzed with 10% H_2SO_4 and methanol under reflux for 4 h to give 1 in 88% yield; bp 180 °C/0.5 Torr (Kugelrohr). IR (KBr film); 3400, 1700 cm^{-1}. NMR (60 MHz, CCl_4); δ 3.56 (2H, s), 3.67 (H, m), 4.20 (2H, s), 7.13 (5H, m).
5. R. Ikan, R. Gottlieb, E. D. Bergmann, and J. Ishay, *J. Insect. Physiol.*, 15, 1709 (1969). For the synthesis of the pheromone; a) J. L. Coke and A. B. Richon, *J. Org. Chem.*, 41, 3516 (1976); b) W. H. Pirkle and P. E. Adams, *ibid.*, 44, 2169 (1979); c) G. Solladié and F. M. Moghadam, *ibid.*, 47, 91 (1982); d) S. Servi, *Tetrahedron Lett.*, 24, 2023 (1983).
6. $[\alpha]_D^{23}$ +49.8° (c 1.00, $CHCl_3$).
7. Although the highest value of the specific rotation data was reported by Pirkle as $[\alpha]_D^{25}$ +57.2° (95 ± 5% ee), our sample derived from the optically pure glycol 2 shows $[\alpha]_D^{23}$ +63.9° (c 1.186, $CHCl_3$); bp 115 °C/0.15 Torr (Kugelrohr). W. H. Pirkle and P. L. Rinold, *J. Org. Chem.*, 43, 3803 (1978).
8. (*S*)-3-Phenylthio-1,2-propanediol (2); A suspention of water (80 ml), sucrose (5 g) and the Baker's yeast (Oriental yeast Co.) (9 g), was stirred for 30 min at 23 °C, then an ethanol solution (18 ml) of 1 (0.364 g, 2.0 mmol) and a aq. solution (18 ml) of sucrose (12 g) were added slowly to the suspention using the sylinge pump over a period of 3 h, at the same time. After stirring for 24 h, the mixture was filtered through a celite pat. The filtrate was extracted with ethyl acetate and was evaporated in vacuo. Purification on silica-gel TLC gave 2 in 90% yield; mp 80 ∿ 81 °C, $[\alpha]_D^{23}$ +16.1° (c 0.941, EtOH). Recrystalization from benzene 3 or 4 times gave optically pure 2 in 63% yield; mp 89 ∿ 90 °C, $[\alpha]_D^{23}$ +20.7° (c 0.996, EtOH). IR (KBr film); 3200, 1550, 1060, 1000, 850, 670 cm^{-1}. NMR (60 MHz, $CHCl_4$); δ 2.87 (2H, m), 3.00 (2H, d, J = 6 Hz), 3.67 (2H, m), 7.27 (5H, m).
9. Phenyl (*S*)-glycidyl sulfide (3); A solution of *p*-toluenesulfonyl chloride (5.64 mmol) in CH_2Cl_2 (6.0 ml) was added at 0 °C to a solution of optically pure glycol 2 (4.7 mmol) and pyridine (8.5 ml), and then stirred at room temperature for 12 h. 3-Phenylthio-2-hydroxy-1-tosyloxypropane was obtained in 91% yield. Treatment of the monotosylate (2.0 mmol) with a methanolic solution (4.0 ml) of NaOH (2.2 mmol) at -10 °C for 4 h to afford the glycidyl sulfide 3 in 81% yield; bp 120 °C/0.55 Torr (Kugelrohr), $[\alpha]_D^{23}$ -34.1° (c 1.06, $CHCl_3$). IR (KBr film); 1090, 1030, 830 cm^{-1}. NMR (60 MHz, CCl_4); δ 2.66 ∿ 2.90 (2H, m), 3.23 (2H, m), 7.57 (m, 5H).
10. C. Huynh, F. D. Boumechal, and G. Linstrumelle, *Tetrahedron Lett.*, 1503 (1979).
11. J. R. Shanklin, C. R. Johnson, J. Ollinger, and R. H. Coates, *J. Am. Chem. Soc.*, 95, 3429 (1973).
12. T. Kogure and E. L. Eliel, *J. Org. Chem.*, 49, 576 (1984).

(Received in Japan 16 October 1984)