

(S)- β,ω -Dihydroxyalkyl Phenyl Sulfones. Synthesis by Bakers' Yeast Reduction
and Use as Precursors of Optically Active Lactones

Toshio SATO, Yoshiyuki OKUMURA, Junichi ITAI, and Tamotsu FUJISAWA*
Chemistry Department of Resources, Mie University, Tsu, Mie 514

The enantioselective reduction of ω -hydroxy- β -ketoalkyl phenyl sulfones with bakers' yeast gives (S)- ω,β -dihydroxyalkyl phenyl sulfones, which are convenient precursors for optically active lactones as shown in the synthesis of (R)-4-hexanolide and (R)-umbelactone.

Asymmetric reduction of ketones with bakers' yeast is increasingly being recognized as a valuable approach to the synthesis of optically active natural products because of easy availability and handling of bakers' yeast.¹⁾ However, the reduction does not always afford alcohols with desired configuration in satisfactory enantiomeric excess. Recently, we have demonstrated that introduction of sulfur functional group to ketones is an effective way both for the stereocontrol in the enantioselective reduction with bakers' yeast and for further manipulation of the reduction products as a chiral building block into natural products.²⁾ In our previous paper, the reduction of 3-phenylthio-1-hydroxy-2-propanone was described to give (S)-3-phenylthio-1,2-propanediol which was a useful trifunctional chiral building block for a variety of optically active secondary alcohols and α -alkoxy aldehydes.^{2b,c)} Here we wish to present new chiral building blocks of (S)- β,ω -dihydroxyalkyl phenyl sulfones (2) from ω -hydroxy- β -ketoalkyl phenyl sulfones (1). Phenylsulfonyl group is more convenient for α -alkylation *via* its α -carbanion and for reductive removal than phenylthio group.³⁾ Although the bakers' yeast-mediated reduction of several β -ketoalkyl phenyl sulfones has been reported to give (S)- β -hydroxy phenyl sulfones,⁴⁾ carbon extension of the alkyl group causes drastic decrease of optical purity of the products.^{4c,d,e)} We have found that the introduction of hydroxyl group at the ω -position of β -keto sulfone not only improves the enantioselectivity but is also effectively utilized in conversion of the products into optically active lactones such as (R)-4-hexanolide (3) and (R)-umbelactone (4).

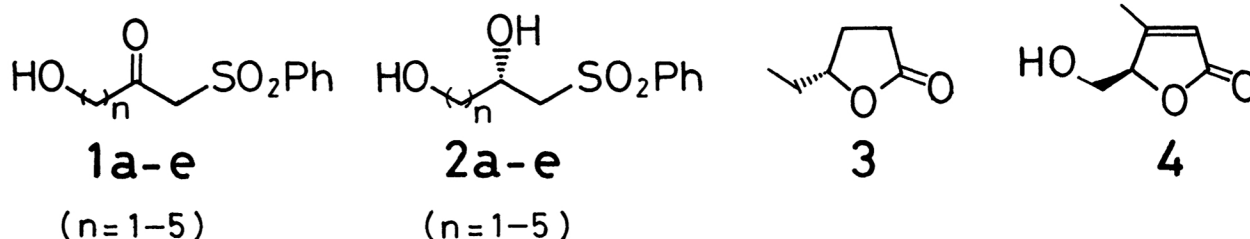


Table 1. The Bakers' Yeast Reduction of β -Keto Sulfone 1 to β,ω -Dihydroxy Sulfone 2

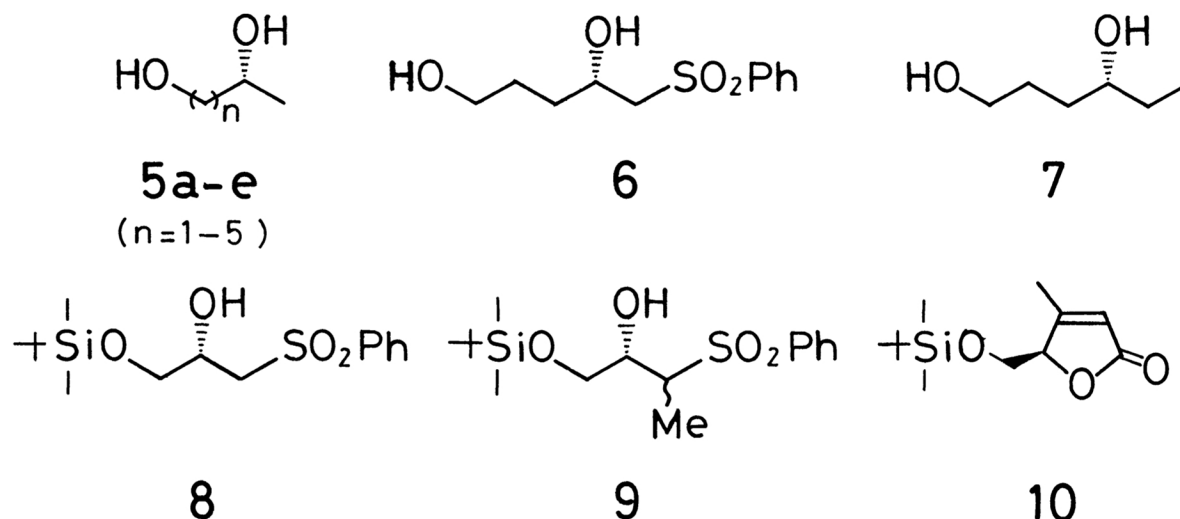
Entry	β -Keto sulfone 1 n	Time/d	Yield/%	%ee ^{c)}	$[\alpha]_D^{23d)}/^\circ$	Config.
1	1	1	87	99 ^{a)}	+21.1 (c 1.00)	S
2	2	7 ^{b)}	42	94	-3.10 (c 1.10)	S
3	3	10 ^{b)}	74	93 ^{a)}	-3.37 (c 1.02) ^{e)}	S
4	4	6 ^{b)}	39	96	-3.71 (c 1.13)	S
5	5	4 ^{b)}	84	72	-3.41 (c 1.06)	S

a) Recrystallization yielded optically pure 2. b) Every three days, yeast 2.5 g, saccharose 3 g, water 25 ml per 1.0 mmol of β -keto sulfone were added. c) Determined by HPLC analysis of the corresponding di-MTPA ester. d) Measured in EtOH. e) Measured with 578 nm.

The substrate of 1-hydroxy-3-phenylsulfonyl-2-propanone (1a) was prepared in 74% yield by oxidation of 1-acetoxy-3-phenylthio-2-propanone^{2b)} with m-chloroperbenzoic acid followed by hydrolysis, and 1b-e were readily obtained by the reaction of the dianion of methyl phenyl sulfone with the corresponding β -, γ -, δ -, and ϵ -lactones.⁵⁾

A typical procedure for the bakers' yeast reduction is as follows: A mixture of 18 g of saccharose and 15 g of bakers' yeast (Oriental Yeast Co.) in 150 ml of water was stirred for 30 min at room temperature, then 5 ml of an ethanol solution of 1a (3.0 mmol) was added to the yeast suspension. The reaction was monitored by silica-gel TLC analysis until the disappearance of the starting ketone. The reaction mixture was stirred for ca. one day at room temperature. After the usual workup, purification by silica-gel column chromatography (AcOEt) gave (S)-3-phenylsulfonyl-1,2-propanediol (2a) in 87% yield.

The result of the yeast reduction of 1 is summarized in Table 1. Optical purity of the product 2 was determined by HPLC analysis of the di-MTPA ester of 2.⁶⁾ The absolute configuration of 2a was defined to be S by comparison of the sign of rotation with that of the authentic sample obtained by oxidation of (S)-3-phenylthio-1,2-propanediol.^{2b)} Reductive removal of phenylsulfonyl group from 2b-e with Ra-Ni gave diols 5b-e of which rotation values were coincident with those of reported diols⁷⁾ or authentic (R)-5e.⁸⁾ As listed in Table 1, all ω -hydroxy- β -keto sulfones 1 gave the (S)- β,ω -dihydroxy sulfones 2. Particularly, 1a was reduced to the diol 2a in one day in 99%ee (entry 1). Although the reduction required a long time according to the extension of the alkyl chain 1b-e, the corresponding diol 2b-d showed high optical purity more than 93%ee (entries 2-4) except 2e (72%ee)(entry 5). Furthermore, recrystallization of 2a from ethyl acetate and 2c from diethyl ether readily afforded (S)-2a and (S)-2c in optically pure form, $[\alpha]_D^{23}$ +21.2° (c 1.00), mp 109 °C and $[\alpha]_D^{23}$ -4.00° (c 1.00), mp 57 °C, respectively. Phenylsulfonyl group seems to be superior to phenylthio group for improvement of the enantioselectivity in the yeast reduction, i.e., 99%ee for 1a and 78%ee for 3-phenylthio-1-hydroxy-2-propanone.^{2b)} The substitution of the hydroxyl group at the



end of alkyl chain remarkably enhanced the enantioselectivity in the bakers' yeast reduction as compared with the following results.⁹⁾ 1-Phenylsulfonyl-2-propanone, -2-butanone, and -2-pentanone furnished the corresponding (S)-alcohols with 95,^{4c)} 60,^{4d)} and 46%ee,^{4e)} respectively.

Optically active β,ω -dihydroxyalkyl phenyl sulfones 2 obtained by the above method are versatile chiral building blocks possessing two different functional groups at both ends of the carbon chain. The utility of the present method was demonstrated in the synthesis of (R)-4-hexanolide (3) and (R)-umbelactone (4). The lactone (R)-3, which was isolated and identified as a component of the pheromone secreted by female dermestid beetle *Trogoderma glabrum*,¹⁰⁾ was synthesized from optically pure 2c. By utilization of the sulfonyl group, α -methylation *via* the trianion of 2c (3 eq. MeLi at $-78^\circ\text{C} \rightarrow -10^\circ\text{C}$, then methyl iodide $-78^\circ\text{C} \rightarrow 0^\circ\text{C}$) gave carbon homologated sulfone 6 in 81% yield. Reductive removal of sulfonyl group with Ra-Ni (W-4) gave (R)-1,4-hexanediol (7) in 79% yield, $[\alpha]_D^{23} +13.4^\circ$ (c 0.21, $^i\text{PrOH}$), lit.¹¹⁾ $[\alpha]_D +13.0^\circ$ ($^i\text{PrOH}$), followed by selective oxidation of primary hydroxyl group of 7 with Fétizon reagent¹²⁾ to afford desired 3 in 80% yield, $[\alpha]_D^{23} +50.9^\circ$ (c 0.42, MeOH), lit.¹³⁾ $[\alpha]_D^{21} +53.1^\circ$ (MeOH).

(R)-Umbelactone (4) was isolated from *Memycelon Umbelatum* Burm.¹⁴⁾ The crude extracts of this plant showed activity against Ranikhe disease virus and exhibited spasmolytic and antiamphetamine activity.¹⁵⁾ Optically pure 2a was converted into 4 as follows. Protection of the primary hydroxyl group as a t-butyldimethylsilyl ether and methylation *via* the dianion of β -hydroxy sulfone 8 gave 9 in 79% yield. Further, treatment of the dianion of 9 with sodium iodoacetate,¹⁶⁾ lactonization, and elimination of phenylsulfonyl group with triethylamine furnished α,β -unsaturated γ -lactone 10, $[\alpha]_D^{23} +54.9^\circ$ (c 0.85, CHCl_3), in 33% yield. Finally desilylation of 10 with hydrofluoric acid gave (R)-umbelactone 4 in 96% yield, $[\alpha]_D^{23} +11.9^\circ$ (c 1.92, CHCl_3), mp 64°C , lit.¹⁷⁾ $[\alpha]_D^{20} +11.7^\circ$ (CHCl_3), mp $62-64^\circ\text{C}$.

Thus, introduction of both hydroxyl and sulfonyl groups into ketone remarkably improves the enantioselectivity of bakers' yeast reduction to afford (S)- β,ω -dihydroxyalkyl phenyl sulfones 2, which are useful trifunctional chiral synthons of optically active natural products.

References

- 1) C. J. Sih and C.-S. Chen, *Angew. Chem., Int. Ed. Engl.*, **23**, 570 (1984); T. Fujisawa, T. Sato, and T. Itoh, *Yuki Gosei Kagaku Kyokai Shi*, **44**, 519 (1986).
- 2) a) T. Fujisawa, T. Itoh, and T. Sato, *Tetrahedron Lett.*, **25**, 5083 (1984); b) T. Fujisawa, T. Itoh, M. Nakai, and T. Sato, *ibid.*, **26**, 771 (1985); c) T. Itoh, A. Yoshinaka, T. Sato, and T. Fujisawa, *Chem. Lett.*, **1985**, 1679; d) T. Fujisawa, E. Kojima, T. Itoh, and T. Sato, *ibid.*, **1985**, 1751; e) *idem.*, *Tetrahedron Lett.*, **26**, 6089 (1985); f) T. Itoh, T. Sato, and T. Fujisawa, *Nippon Kagaku Kaishi*, **1987**, 1413; g) T. Fujisawa, E. Kojima, and T. Sato, *Chem. Lett.*, **1987**, 2227; h) T. Sato, K. Hanayama, and T. Fujisawa, *Tetrahedron Lett.*, **29**, 2197 (1988).
- 3) P. D. Magnus, *Tetrahedron*, **33**, 2019 (1977).
- 4) a) K. Nakamura, K. Ushio, S. Oka, A. Ohno, and S. Yasui, *Tetrahedron Lett.*, **25**, 3979 (1984); b) R. L. Crumbie, B. S. Deol, J. E. Nemorin, and D. D. Ridley, *Aust. J. Chem.*, **31**, 1965 (1978); c) S. Iriuchijima and N. Kojima, *Agric. Biol. Chem.*, **42**, 451 (1978); d) A. P. Kozikowski, B. B. Mugrage, C. S. Li, and L. Felder, *Tetrahedron Lett.*, **27**, 4817 (1986); e) R. Tanikaga, K. Hosoya, and A. Kaji, *Synthesis*, **1987**, 389; *J. Chem. Soc., Perkin Trans. 1*, **1987**, 1799.
- 5) M. C. Mussatto, D. Savoia, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.*, **45**, 4002 (1980); S. Cavicchioli, D. Savoia, C. Trombini, and A. Umani-Ronchi, *J. Org. Chem.*, **49**, 1246 (1984).
- 6) J. A. Dale, D. L. Dull, and H. S. Mosher, *J. Org. Chem.*, **34**, 2543 (1969).
- 7) S. Murakami, T. Harada, and A. Tai, *Bull. Chem. Soc. Jpn.*, **53**, 1356 (1980); C. H. Bolton, A. B. Foster, M. Stacey, and J. M. Webber, *J. Chem. Soc.*, **1961**, 4831; T. Ishida and K. Wada, *J. Chem. Soc., Chem. Commun.*, **1975**, 209.
- 8) The authentic compound (R)-5, $[\alpha]_D^{23} -13.9^\circ$ (c 0.66, EtOH), was prepared from methyl (R)-3-hydroxybutylate (96%ee) *via* the reaction of (R)-1-bromo-3-tetrahydropyranyloxybutane with the Grignard reagent of 3-chloropropanol, see K. Mori and K. Tanida, *Tetrahedron*, **37**, 3221 (1981) and G. Cahiez, A. Alexakis, and J. F. Normant, *Tetrahedron Lett.*, **1978**, 3013.
- 9) Bakers' yeast reduction of 1-chloro-3-phenylsulfonyl-2-propanone was reported to give the corresponding (R)-alcohol with 84%ee.^{4e)}
- 10) R. G. Yarger, R. M. Silverstein, and W. E. Burkholder, *J. Chem. Ecol.*, **1**, 323 (1975).
- 11) R. J. Crawford, V. Vukov, and H. Tokunaga, *Can. J. Chem.*, **51**, 3718 (1973).
- 12) V. Balogh, M. Fétizon, and M. Golfier, *J. Org. Chem.*, **36**, 1339 (1971).
- 13) K. Mori, H. Mori, and T. Sugai, *Tetrahedron*, **41**, 919 (1985).
- 14) S. K. Agarwal and R. P. Rastogi, *Phytochemistry*, **17**, 1663 (1978).
- 15) M. L. Dhar, M. M. Dhar, B. N. Dhawan, B. N. Mehrotra, and C. Ray, *Indian J. Exp. Biol.*, **6**, 241 (1968).
- 16) K. Tanaka, K. Ootake, K. Imai, N. Tanaka, and A. Kaji, *Chem. Lett.*, **1983**, 633.
- 17) R. M. Ortuño, J. Bigorra, and J. Font, *Tetrahedron*, **43**, 2199 (1987).

(Received June 22, 1988)