Synthesis of (*Rc*,*Ss*)-1,1,1-Trifluoro-3-(*p*-tolylsulfinyl)-2-propanol by an Asymmetric Reduction with a Yeast, *Yamadazyma farinosa*, as a Key-step

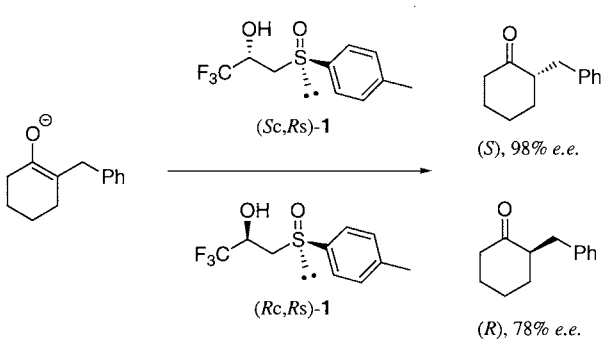
Atsushi Sakai, Mikio Bakke, Hiromichi Ohta, Hiroshi Kosugi,† and Takeshi Sugai*
Department of Chemistry, Keio University, 3-14-1 Hiyoshi, Yokohama 223-8522
†*Institute for Chemical Research, Tohoku University, 2-1-1 Katahira, Sendai 980-8577*

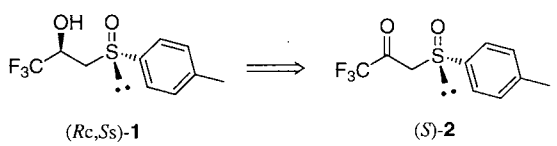
(Received August 30, 1999; CL-990744)

(*Rc*,*Ss*)-1,1,1-trifluoro-3-(*p*-tolylsulfinyl)-2-propanol (>99% *e.e.*), an important reagent for the asymmetric protonation of substituted enolates, was prepared (70%) from (*S*)-methyl *p*-tolyl sulfoxide. The stereoselectivity of the *Yamdazyma farinosa*-catalyzed reduction of carbonyl groups, the key step for the introduction of an asymmetric carbon, was greatly affected by the stereochemistry of the asymmetric sulfur atom. The reduction of (*S*)-1,1,1-trifluoro-3-(*p*-tolylsulfinyl)-2-propanone proceeded smoothly and in a quite stereoselective manner to give the desired compound, while a 76 : 24 mixture of (*Rc*,*Rs*)- and (*Sc*,*Rs*)-isomers was obtained from the substrate with the opposite (*R*)-configuration.

Asymmetric protonation of enolates is an excellent way for the preparation of enantiomerically enriched forms of carbonyl compounds.[1] Among the chiral proton sources, 1,1,1-trifluoro-3-(*p*-tolylsulfinyl)-2-propanol (**1**) have been developed by one of the authors (H. K.)[2,3] The importance of the combination of the two chiral centers has been advocated. For example, in a matched case, the asymmetric yield was very high; however, in a mismatched case, the enantiofacial selectivity of protonation was not satisfactory, as shown below. Needless to say, the importance of both enantiomeric forms of reagents has been well recognized, so as to secure both enantiomers of α-substituted ketones. Here we report an expeditious route to (*Rc*,*Ss*)-**1**, the opposite enantiomer of (*Sc*,*Rs*)-**1**, whose chiral centers are arranged as a matched pair.

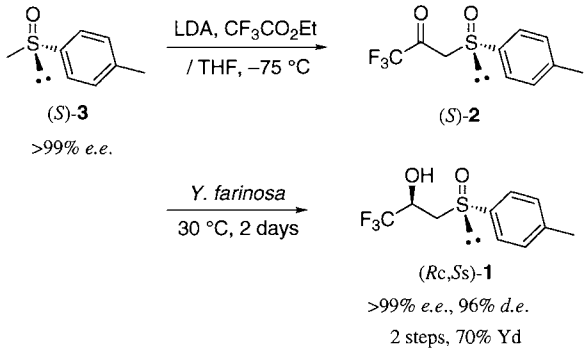
So far, chiral ß-hydroxy sulfoxides, for example, isomers with (*R**c,*S**s)-stereochemistry, have been synthesized by means





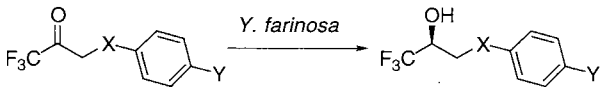
of the diastereoselective reduction of the enantiomerically enriched form of ß-keto sulfoxides with reducing agent such as DIBAL-H.[4,5] On the other hand, for the introduction of the second chiral center, the results established in our previous work led us to the use of the yeast-catalyzed reduction with *Yamadazyma farinosa* IFO 10896,[6,7] whose reduction proceeds in an enantiofacially selective manner, according to the so-called '*anti*-Prelog' rule.

Toward this end, (*S*)-methyl *p*-tolyl sulfoxide (**3**), which was prepared by enantioselective *t*-BuOOH-mediated oxidation of the corresponding racemate catalyzed by BINOL-Ti,[8] was converted to (*S*)-**2** in a conventional manner.[9] Treatment of (*S*)-**2** with incubated cells of *Y. farinosa* provided (*Rc*,*Ss*)-**1** and (*Sc*,*Ss*)-**1** in a highly selective manner (98 : 2) in 70% yield from (*S*)-**3**.[10] The desired (*Rc*,*Ss*)-isomer could be isolated in pure state by silica gel column chromatography.[4,11]



We became interested in the effect of the pre-existing oxygen functionality and chirality on the sulfur atom,[cf.12,13] and the results are summarized in the Table 1. The reduction of the opposite enantiomer of the substrate, (*R*)-**2**, afforded a 76 : 24 mixture of (*Rc*,*Rs*)- and (*Sc*,*Rs*)-**1** (entry 2). The difference was in good accordance with the results observed by Iriuchijima and Fujisawa namely, that the whole cell enzyme system in baker's yeast showed a contrasting action toward the enantiomers of β-sulfinyl ketones.[12,13] It was interesting that the corresponding sulfone (**4**) showed a similar low selectivity to that for (*R*)-**2** (entry 3). Obviously the introduction of the oxygen atom in *pro*-(*R*) orientation had a lowering effect on the enantiofacial selectivity (entry 1–4). It is noteworthy that the present observation on the influence of stereochemistry was the complementary result with that of baker's yeast-catalyzed reduction. In the latter case, *pro*-(*S*) oxygen atom had such a lowering effect. These results may be ascribable to the contribution of plural enzymes in the whole cell of the yeast strain, which has been revealed in the case of baker's yeast-catalyzed reaction.[14]

Table 1.



Entry	Substrate				Product	
		X	Abs. config.	Y	Yield / %	Enantiofacial selectivity
1	**2**	S = O	S	CH_3	80	98 : 2
2	**2**	S = O	R	CH_3	86	76 : 24
3	**4**	SO_2	—	CH_3	70	75 : 25
4	**5**[a]	S	—	H	72	93 : 7

[a]See Ref. 6,15

In conclusion, (*Rc*,*Ss*)-1,1,1-trifluoro-3-(*p*-tolylsulfinyl)-2-propanol (**1**, >99% *e.e.*) was prepared in 70% yield through two steps from (*S*)-methyl *p*-tolyl sulfoxide (**3**), by a *Yamadazyma farinosa*-catalyzed reduction as the key step.

The authors thank Professor Sakae Uemura of graduate School of Engineering, Kyoto University for valuable suggestions. This work was accomplished as "Science and Technology Program on Molecules, Supra-Molecules and Supra-Structured Materials" of an Academic Frontier Promotional Project and was also supported by a Grant-in-Aid for Scientific Research (No. 10125238).

References and Notes

1 Review: D. Hoppe and T. Hense, *Angew. Chem., Int. Ed. Engl.*, **36**, 2283 (1997); H. Ohta, *Bull. Chem. Soc. Jpn.*, **70**, 2895 (1997); K. Fuji and T. Kawabata, *Chem. Eur. J.*, **4**, 373 (1998); Recent issues: T. Hirata, K. Shimada, D. Ohba, N. Furuya, and S. Izumi, *Tetrahedron: Asymmetry*, **8**, 2671 (1997); A. Yanagisawa, H. Inanami, and H. Yamamoto, *Chem. Commun.*, **1998**, 1573; Y. Nakamura, S. Takeuchi, Y. Ohgo, M. Yamaoka, A. Yoshida, and K. Mikami, *Tetrahedron*, **55**, 4595 (1999).

2 H. Kosugi, M. Abe, R. Hatsuda, H. Uda, and M. Kato, *Chem. Commun.*, **1997**, 1857; H. Kosugi, K. Hoshino, and H. Uda, *Tetrahedron Lett.*, **39**, 6861 (1997).

3 G. Asensio, P. A. Aleman, L. R. Domingo, and M. Medio-Simón, *Tetrahedron Lett.*, **39**, 3277 (1998); G. Asensio, A. Alemán, and M. Medio-Simón, *Tetrahedron: Asymmetry*, **9**, 4073 (1998).; G. Asensio, A. Cuenca, P. Gaviña, and M. Medio-Simón, *Tetrahedron Lett.*, **40**, 3939 (1999).

4 P. Bravo, M. Frigerio, and G. Resnati, *Synthesis*, **1988**, 955.

5 H. Kosugi, H. Konta, and H. Uda, *J. Chem. Soc., Chem. Commun.*, **1985**, 211; G. Solladié, G. Damailly, and C. Greck, *Tetrahedron Lett.*, **26**, 435 (1985); G. Solladié, G. Demailly, and C. Greck, *J. Org. Chem.*, **50**, 1552 (1985); G. Solladié, G. Demailly, and C. Greck, *J. Org. Chem.*, **50**, 1912 (1985).

6 T. Sugai and H. Ohta, *Agric. Biol. Chem.*, **54**, 1577 (1990); N. Mochizuki, H. Yamada, T. Sugai, and H. Ohta, *Bioorg. Med. Chem.*, **1**, 71 (1993); T. Sugai, O. Katoh, and H. Ohta, *Tetrahedron*, **51**, 11987 (1995); H. Ikeda, E. Sato, T. Sugai, and H. Ohta, *Tetrahedron*, **52**, 8113 (1996); T. Sugai, K. Hamada, T. Akeboshi, H. Ikeda, and H. Ohta, *Synlett*, **1997**, 983.

7 Y. Ohtsuka, O. Katoh, T. Sugai, and H. Ohta, *Bull. Chem. Soc., Jpn.*, **70**, 483 (1997).

8 N. Komatsu, Y. Nishibayashi, T. Sugita, and S. Uemura, *Tetrahedron Lett.*, **33**, 5391 (1992); N. Komatsu, M. Hashizume, T. Sugita, and S. Uemura, *J. Org. Chem.*, **58**, 4529 (1993).

9 P. Bravo, E. Piovosi, and G. Resnati, *Synthesis*, **1986**, 579.

10 Experimental procedure and properties of (*Rc*,*Ss*), (*Rc*,*Rs*)-3,3,3-trifluoro-1-(*p*-tolylsulfinyl)-2-propanol (**1**) and (*R*)-3,3,3-trifluoro-1-(*p*-tolylsulfonyl)-2-propanol (**6**): *Yamadazyma farinosa* IFO 10896 was pre-incubated according to the reported procedure.[6] The wet cells (10 g) were re-suspended in a phosphate buffer solution (pH 6.5, 0.1 M, 50 ml) in a 500-ml shaking culture (Sakaguchi) flask with the substrate (*Ss*)-**2** [250 mg, 1.00 mmol, 0.5% (w/v)]. After glucose (2.5 g) was added, the air inside the flask was purged with argon, and the flask was equipped with a balloon charged with argon. The flask was shaken at 30 °C on a reciprocal shaker for 2 days. The cell mass was removed by a filtration with Celite. The filtrate was extracted with ethyl acetate several times and the cell mass was thoroughly washed with ethyl acetate. The combined extracts and washings were washed with brine, dried with sodium sulfate and concentrated *in vacuo*. ^{1}H-NMR spectrum of the crude mixture showed that the reduction was completed. The crude residue was purified by silica gel column chromatography (4 g). Elution with hexane / ethyl acetate (10 / 1) afforded **1** (177 mg, 70%). The *d.e.* of the product was confirmed by HPLC analysis. HPLC (column, Senshu Pak PEGASIL silica 60-5, 4.6 mm × 250 mm; solvent, hexane / 2-propanol = 9 / 1; flow rate 5 ml/min): t_R = 12.8 min [(*Rc*,*Ss*), 98.1%], 16.9 min [(*Sc*,*Ss*), 1.9%]. Accordingly, the *d.e.* of (*Rc*,*Ss*)-**1** was estimated to be 96.2%. Pure (*Rc*,*Ss*)-**1** was obtained by a further elaborated chromatographic purification. $[\alpha]_D^{26}$ –232.7 (*c* 1.06, $CHCl_3$) [lit.[4] $[\alpha]_D^{20}$ +260 (*c* 1.1, $CHCl_3$) for (*Sc*,*Rs*)-isomer]. ^{1}H NMR (270 MHz) δ = 2.45 (s, 3H), 2.84 (dd, *J* = 13.5, 2.0 Hz, 1H), 3.19 (dd, *J* = 13.5, 10.8 Hz, 1H), 4.50-4.54 (m, 1H), 4.88 (d, *J* = 3.6 Hz, 1H), 7.39 (d, *J* = 8.1 Hz, 2H), 7.55 (d, *J* = 8.1 Hz, 2H).
The reduction of (*Rs*)-**2** as described above afforded a mixture of (*Rc*,*Rs*)-**1** and (*Sc*,*Rs*)-**1** (214.4 mg, 85.3%). Based on the HPLC analysis of this, the *d.e.* of (*Rc*,*Rs*)-**1** was estimated to be 52.0%. The diastereomeric mixture was separated by silica gel column chromatography (15 g). Elution with hexane / 2-propanol (20 / 1) afforded two pure diastereomers, (*Rc*,*Rs*)-**1** (152.3 mg) and (*Sc*,*Rs*)-**1** (50.6 mg), respectively. (*Rc*,*Rs*)-**1**, $[\alpha]_D^{26}$ +175.6 (*c* 1.03, $CHCl_3$) [lit.[4] $[\alpha]_D^{20}$ +196 (*c* 1.0, $CHCl_3$)]. ^{1}H NMR (270 MHz) δ = 2.44 (s, 3H), 3.02 (dd, *J* = 13.3, 3.1 Hz, 1H), 3.10 (dd, *J* = 13.3, 9.3 Hz, 1H), 4.36 (d, *J* = 2.6 Hz, 1H), 4.66-4.71 (m, 1H), 7.38 (d, *J* = 8.3 Hz, 2H), 7.58 (d, *J* = 8.3 Hz, 2H). (*Sc*,*Rs*)-**1**, $[\alpha]_D^{26}$ +237.4 (*c* 1.04, $CHCl_3$) [lit.[4] $[\alpha]_D^{20}$ +260 (*c* 1.1, $CHCl_3$)]. Its ^{1}H NMR spectrum was identical with that of (*Rc*,*Ss*)-**1**.
The reduction of 3,3,3-trifluoro-1-(*p*-tolylsulfonyl)-2-propanone (**4**) as described above afforded (*R*)-alcohol **6** (176.2 mg, 70.1%). $[\alpha]_D^{28}$ –5.71 (*c* 1.13, $CHCl_3$). ^{1}H NMR (400 MHz) δ = 2.48 (s, 3H), 3.35-3.43 (m, 2H), 3.57 (d, *J* = 3.4 Hz, 1H), 4.51-4.57 (m, 1H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.83 (d, *J* = 8.3 Hz, 2H). An authentic sample with (*R*)-configuration was prepared from (*Rc*,*Ss*)-**1** by oxidation with H_2O_2. $[\alpha]_D^{28}$ –11.3 (*c* 1.02, $CHCl_3$). The enantiofacial selectivity was estimated to be in the ratio 75 : 25, by the comparison of the values of optical rotation, as the direct HPLC analyses with chiral stationary phases (ChiralCells) were unsuccessful. Furthermore, due to the steric hindrance as well as the low nucleophilic nature of secondly alcohol caused by neighboring CF_3 and SO_2 groups, the diastereomers of corresponding MTPA esters could not express precisely the enantiomeric ratio of the alcohol **6**.

11 Unpublished results (H. K.)

12 S. Iriuchijima and N. Kojima, *Agric. Biol. Chem.*, **42**, 451 (1978).

13 T. Sato, T. Itoh, and T. Fujisawa, *Tetrahedron Lett.*, **28**, 5677 (1987); T. Fujisawa, A. Fujimura, and T. Sato, *Bull. Chem. Soc. Jpn.*, **61**, 1273 (1988).

14 W.-R. Shieh, A. S. Gopalan, and C. J. Sih, *J. Am. Chem. Soc.*, **107**, 2993 (1985); J. Heidlas, K.-H. Engel, and R. Tressl, *Eur. J. Biochem.*, **172**, 633 (1988); K. Nakamura, S. Kondo, Y. Kawai, N. Nakajima, and A. Ohno, *Biosci. Biotechnol. Biochem.*, **58**, 2236 (1994).

15 *Geotrichum candidum* effectively worked for the reduction of **5**: K. Nakamura, T. Matsuda, M. Shimizu and T. Fujisawa, *Tetrahedron*, **54**, 8393 (1998); The alcohol as enantiomericaly enriched form was also prepared by a lipase-catalyzed kinetic resolution: M. Shimizu, K. Sugiyama, and T. Fujisawa, *Bull. Chem. Soc. Jpn.*, **69**, 2655 (1996).