Enantioselective Synthesis of the Novel Chiral Sulfoxide Derivative as a Glycogen Synthase Kinase 3β Inhibitor

Morihisa Saitoh,* Jun Kunitomo, Eiji Kimura, Toru Yamano, Fumio Itoh, and Masakuni Kori

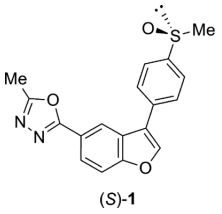
Medicinal Chemistry Research Laboratories, Pharmaceutical Research Division, Takeda Pharmaceutical Co., Ltd.; 2–17–85 Jusohonmachi, Yodogawa-ku, Osaka 532–8686, Japan.

Received May 1, 2010; accepted June 18, 2010; published online June 28, 2010

Glycogen synthase kinase 3β (GSK-3β) inhibitors are expected to be attractive therapeutic agents for the treatment of Alzheimer's disease (AD). Recently we discovered sulfoxides (*S*)-1 as a novel GSK-3β inhibitor having *in vivo* efficacy. We investigated practical asymmetric preparation methods for the scale-up synthesis of (*S*)-1. The highly enantioselective synthesis of (*S*)-1 (94% ee) was achieved by titanium-mediated oxidation with D-(−)-diethyl tartrate on gram scale.

Key words glycogen synthase kinase 3β; enantioselective oxidation; Alzheimer's disease

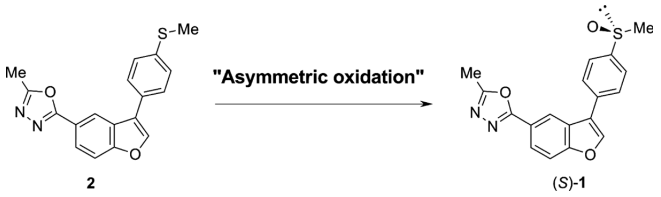
Alzheimer's disease (AD) is a neurodegenerative disorder manifested by cognitive and memory deterioration, progressive impairment of the activities involved in daily living, and behavioral disturbances. Glycogen synthase kinase 3β (GSK-3β) inhibitors are thought to be attractive agents for the treatment of AD.[1,2] Recently we reported a novel GSK-3β inhibitor (Fig. 1) and this compound significantly reduced tau phosphorylation in a mouse model.[3]



(*S*)-**1**

Fig. 1. Structure of (*S*)-**1**

Compound (*S*)-**1** initially was obtained by the resolution of racemic-**1** using chiral high performance liquid chromatography (HPLC). Although separation by HPLC was a sufficient method for the preparation of small quantities of (*S*)-**1**, large scale production was expected to be problematic for this compound. Thus, we investigated asymmetric synthesis routes for (*S*)-**1**. Among the various methods of asymmetric oxidation for sulfides,[4] the method using a chiral titanium complex derived from a Sharpless reagent reported by Kagan and colleagues[5] is attractive. Our colleagues have previously applied this methodology to the synthesis of optically active lansoprazole.[6] Therefore, we embarked upon optimizing reaction conditions for preparing (*S*)-**1** from prochiral sulfides **2** (Chart 1).



2 (*S*)-**1**

Chart 1. Strategies for Preparation of Sulfoxides (*S*)-**1**

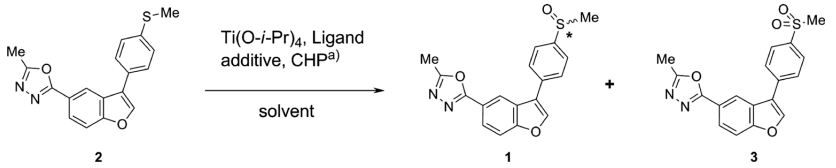
Results and Discussion

The starting material, methyl sulfide **2** was prepared by the 6-step protocol previously reported.[3] Spectroscopic data and X-ray crystal structures confirmed the configuration of (*S*)-**1**.[3] First, we attempted conditions similar to those used for the synthesis of chiral lansoprazole,[6] which used a stoichiometric amount of Ti(O-*i*-Pr)$_4$, (+)-diethyl tartrate (DET) as ligand, cumene hydroperoxide (CHP) as oxidant, and toluene or dichloromethane as solvent, in the presence of water. Because of the difficulty in separating the sulfoxide **1** and sulfone **3**, we used substoichiometric CHP (0.83 eq) relative to sulfide. The condition using toluene as solvent resulted in production of undesired enantiomer with low enantiomeric excess (Table 1, entry 1). We assumed the low enantioselectivity was caused by low solubility of sulfide **2** in toluene. Therefore, we used dichloromethane as solvent and reaction proceeded in a homogenous solution to show improved enantiomeric excess of 66% ee (entry 2). From this result, we used dichloromethane in further investigations. Since (+)-DET resulted in the conversion of sulfide **2** to the undesired (*R*)-**1**, we changed the ligand to (−)-DET. It is known that the amount of water significantly affects the selectivity of this reaction.[5] Although combination of Ti(O-*i*-Pr)$_4$/H$_2$O (1 : 1) is effective in enantioselective oxidation,[7] 0.5 eq of water ensured a good enantiomeric excess for this particular substrate (entries 3—5). Lower temperature was preferred in terms of selectivity and afforded good enantiomeric excess (entries 6—8). However, the reaction rate tended to be slow at low temperatures and reaction was not completed within 24 h at −40 °C (entries 9, 10). Enantioselectivity was not affected by the use of molecular sieves (entry 11).[7] Other ligands such as (−)-dimethyl tartrate (DMT), (−)-diisopropyl tartrate (DIPT) and (*R*)-(+)-1,1′-bi-naphthol (BINOL) were less effective than (−)-DET (entries 12—14). Because a large excess of water and the use of toluene as solvent enhance the enantioselectivity of oxidations with the titanium complex of BINOL,[8] optimized conditions for tartrate derivatives were not considered suitable for the BINOL methodology.

We also tried asymmetric oxidation using vanadyl acetylacetonate (VO(acac)$_2$) and Schiff base ligand **4**,[9] but enantioselectivity was found to be low (Chart 2). Since Schiff bases are known to significantly affect the enantioselectivity of vanadium mediated oxidations,[9] screening of Schiff bases and optimization of reaction conditions were considered to

* To whom correspondence should be addressed. e-mail: Saitoh_Morihisa@takeda.co.jp

Table 1. Enantioselective Oxidation of Sulfide **2**



Entry[a)]	Ligand[b)]	H_2O	Additive	Solvent	Temp.	Time (h)	Yield[c)]			ee of (*S*)-**1**[c)]
							1	**2**	**3**	
1	L-(+)-DET	1.1	—	Toluene	rt	24	—	—	—	32.1[d)]
2	L-(+)-DET	1.1	—	CH_2Cl_2	0 °C	24	—	—	—	66.0[d)]
3	D-(−)-DET	0.5	—	CH_2Cl_2	0 °C	5	65.6	2.9	3.2	86.5
4	D-(−)-DET	2	—	CH_2Cl_2	0 °C	5	39.4	12.1	1.8	41.0
5	D-(−)-DET	0	—	CH_2Cl_2	0 °C	5	70.3	23.9	2.8	85.0
6	D-(−)-DET	0.5	—	CH_2Cl_2	−20 °C	5	66.9	16.0	1.3	90.6
7	D-(−)-DET	0.5	—	CH_2Cl_2	−30 °C	5	83.5	36.0	0.5	92.6
8	D-(−)-DET	0.5	—	CH_2Cl_2	−30 °C	24	80.3	11.9	1.6	93.5
9	D-(−)-DET	0.5	—	CH_2Cl_2	−40 °C	5	36.2	58.5	1.5	92.2
10	D-(−)-DET	0.5	—	CH_2Cl_2	−40 °C	24	60.4	23.0	0.6	94.0
11	D-(−)-DET	0.5	MS3A	CH_2Cl_2	−20 °C	5	57.0	14.3	1.3	91.5
12	D-(−)-DET	0.5	—	CH_2Cl_2	−20 °C	5	56.0	43.6	0.4	57.9
13	D-(−)-DIPT	0.5	—	CH_2Cl_2	−20 °C	5	64.8	25.0	1.8	88.3
14	(*R*)-(+)-BINOL	0.5	—	CH_2Cl_2	−20 °C	5	59.2	32.1	0.7	30.6

a) Cumene hydroperoxide solution (entry 1—13: 0.83 eq, entry 14: 1.05 eq). *b*) DET: diethyl tartrate, DMT: dimethyl tartrate, DIPT: diisopropyl tartrate, BINOL: 1,1′-bi-2-naphthol. *c*) Determined by chiral HPLC. *d*) ee of (*R*)-**1**.

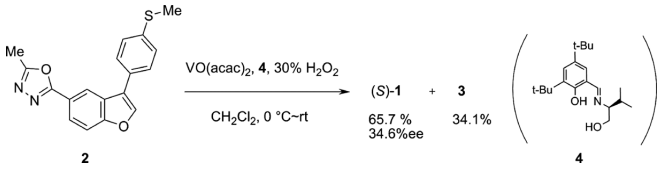


Chart 2. $VO(acac)_2$-Catalyzed Enantioselective Oxidation of Sulfide **2**

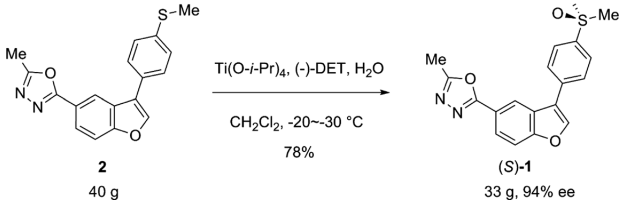


Chart 3. Scale-Up Synthesis of (*S*)-**1**

take enormous efforts, thus we stopped further investigation of using vanadium catalysts.

On the basis of these results obtained above, we applied the best conditions of titanium mediate asymmetric oxidation (Table 1, entry 8, $Ti(O\text{-}i\text{-}Pr)_4/H_2O$ (1 : 0.5), −20 to −30 °C, 24 h) on a larger scale, and the reaction of 40 g of sulfide **2** proceeded well to afford 33 g of (*S*)-**1** in 78% yield and 94% ee (Chart 3).

Conclusion

We developed a practical enantioselective synthesis for the preparation of the novel GSK-3β inhibitor (*S*)-**1**. The optimized amount of water in Kagan's enantioselective oxidation of sulfide enhanced enantioselectivity in the synthesis of (*S*)-**1**. This methodology was also applied for the large scale synthesis and 33 g of (*S*)-**1** with 94% ee was obtained. This scale-up synthesis facilitated further pharmacological and toxicological studies of these compounds. Catalytic asymmetric oxidation is a significant challenge in the future of organic synthesis.

Experimental

Melting points were determined on a Buchi melting point apparatus and were not corrected. All commercially available reagents and solvent were employed without prior purification. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on a Bruker DPX300 (300 MHz) instrument. Chemical shifts are reported as δ values (ppm) downfield from internal tetramethylsilane referenced to the residual solvent peak. Peak multiplicities are expressed as follows. Abbreviations are used as follows: s, singlet; d, doublet; dd, doublet of doublet; m, multiplet. Coupling constants (*J* values) are given in hertz (Hz). Enantiomeric excess and the conversion of yields were all determined by HPLC analysis on a CHIRALPAK AS column (0.5 cm×50 cm, EtOH, 0.4 ml/min) for the conversion of (*S*)-**1**.

General Procedure for Asymmetric Oxidation of Sulfide To a mixture of sulfide **2** (1.0 eq) and H_2O was added a tartrate ester or (*R*)-(+)-1,1′-bi-naphthol (2.6 eq) in solvent (5 ml) and $Ti(O\text{-}i\text{-}Pr)_4$ (1.0 eq), and the solution was stirred for 1 h at room temperature. Then the mixture was cooled, CHP (0.83 eq or 1.05 eq) was added to the solution and was stirred at the same temperature. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The yield and enantiomeric excess of sulfoxide (*S*)-**1** were determined by chiral HPLC.

Vanadium Catalyzed Asymmetric Synthesis (Chart 2) A mixture of $VO(acac)_2$ (1.64 mg, 6.20 μmol), **4** (2.97 mg, 9.30 μmol) in dichloromethane (5 ml) was stirred for 30 min at room temperature, then **2** (0.20 g, 0.62 mmol) was added. The mixture was cooled to 0 °C and was added H_2O_2 (30%, 76 μl, 0.74 mmol) at the same temperature. After stirring for 28 h at 0 °C, the reaction mixture was partitioned between EtOAc and H_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The yield of sulfoxide was 66% and enantiomeric excess was 35% ee (determined by chiral HPLC).

Large Scale Asymmetric Synthesis of (*S*)-1 To a mixture of sulfide **2** (40.0 g, 124 mmol) and H_2O (1.12 ml, 62.1 mmol) was added (−)-DET (53.6 ml, 273 mmol) in dichloromethane (1.2 l) and $Ti(O\text{-}i\text{-}Pr)_4$ (36.7 ml, 124 mmol), and the solution was stirred for 1 h at room temperature. The mixture was cooled to −24 °C, CHP (80%, 19 ml, 103 mmol) was added to the solution, and stirring was continued at −24 °C for 24 h. The reaction mixture was quenched with saturated aqueous Na_2SO_3 solution, the organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. The residue was purified by silica gel (400 g) using EtOAc–MeOH (1/0—9/1) and NH silica gel (500 g) using hexane– tetrahy-

drofuran (THF)(1/2) to give (*S*)-**1** (80%, 94% ee) as a colorless solid. ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 2.65 (3H, s), 2.81 (3H, s), 7.69 (1H, d, J=8.7 Hz), 7.78—7.86 (4H, m), 7.94 (1H, s), 8.08 (1H, dd, J=8.7, 1.9 Hz), 8.48—8.51 (1H, m). $[\alpha]_D^{25}$ −89.9 (c=0.49, MeOH). mp 170—171 °C. t_R=31.8 min.

Acknowledgements The authors thank Mr. Katsuhiko Miwa for HPLC analyses. We also thank Mr. Yuichiro Kondo and Mr. Masayuki Yamashita for discussions about experimental procedures.

References

1) Cohen P., Goedert M., *Nat. Rev. Drug Discov.*, **3**, 479—487 (2004).
2) Martinez A., *Med. Res. Rev.*, **28**, 773—796 (2008).
3) Saitoh M., Kunitomo J., Kimura E., Iwashita H., Uno Y., Onishi T., Uchiyama N., Kawamoto T., Tanaka T., Mol C. D., Dougan D. R., Textor G. P., Snell G. P., Takizawa M., Itoh F., Kori M., *J. Med. Chem.*, **52**, 6270—6286 (2009).
4) Kagan H. B., "Organosulfur Chemistry in Asymmetric Synthesis," ed. by Toru T., Bolm C., Wiley InterScience, New York, 2008, pp. 1—26.
5) Pitchen P., Duñach E., Deshmukh M. N., Kagan H. B., *J. Am. Chem. Soc.*, **106**, 8188—8193 (1984).
6) Kawada M., Yamano T., Taya N., Jpn. Kokai Tokyo Koho JP2001-131172.
7) Zhao S. H., Samuel O., Kagan H. B., *Tetrahedron*, **43**, 5135—5144 (1987).
8) Komatsu N., Hashizume M., Sugita T., Uemura S., *J. Org. Chem.*, **63**, 7624—7626 (1993).
9) Skarżewski J., Ostrycharz E., Siedlecka R., *Tetrahedron: Asymmetry*, **10**, 3457—3461 (1999).