Pergamon

Tetrahedron: Asymmetry, Vol. 8, No. 13, pp. 2109–2114, 1997

Printed in Great Britain
PII: S0957-4166(97)00205-X
0957-4166/97 $17.00 + 0.00

Substrate specificity of the kinetic resolution of sulfides by enantioselective sulfoxide formation

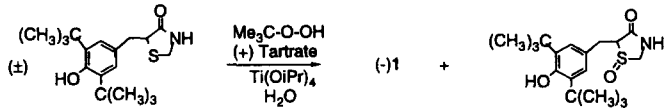
Michael L. Phillips and Jill A. Panetta *

Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis, Indiana, 46285, USA

Abstract: The kinetic resolution of tazofelone (**1**) has been reported. The resolution of this sulfide was accomplished via enantioselective sulfoxide formation with *tert*-Bu hydroperoxide in the presence of a chiral tartrate/titanium complex. The resolution was performed on analogues of compound **1** in order to explore the substrate specificity of the kinetic resolution. These experiments have shown that the success of the enantioselective oxidation of this sulfide by *tert*-Bu hydroperoxide is greatly influenced by the nature of the neighboring amide functionality. © 1997 Elsevier Science Ltd

The asymmetric oxidation of sulfides using a water-modified Sharpless reagent was originally described by Kagan.[1] Many reports on the use of these and similar conditions for the synthesis of chiral sulfoxides have been published.[2] Kinetic resolution resulting from the incomplete oxidation of racemic sulfides by this reagent is therefore possible, but has only been reported in a few cases.[3] Furthermore, partial oxidation of racemic sulfoxides to sulfones can result in a kinetic resolution of the sulfoxide. Substrate specificity of the resolution of some sulfoxides has been briefly described.[4] Here we report the first study on the substrate specificity of the kinetic resolution of a sulfide using this titanium-based catalyst.

The kinetic resolution of tazofelone, (±)5-[[3,5-bis(1,1-dimethyl-ethyl)-4-hydroxyphenyl]methyl]-4-thiazolidinone (**1**) has been previously described by us.[3a] This compound has been shown to protect against acetic acid-induced colitis in rats and has been selected for clinical development for the treatment of inflammatory bowel disease.[5] The resolution of this sulfide was accomplished via enantioselective sulfoxide formation with *tert*-Bu hydroperoxide in the presence of a chiral tartrate/titanium complex (Scheme 1).



1

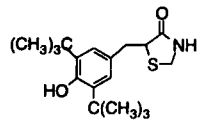
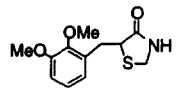
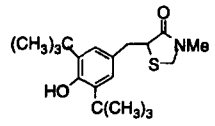
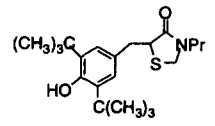
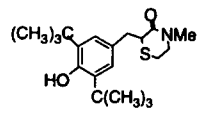
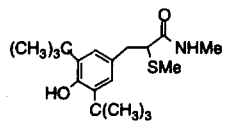
Scheme 1.

Higher enantiomeric excess resulted from increased reaction completion as would be expected. For the simple preparation of each enantiomer for *in vivo* comparison, the reaction was ran to 80% conversion to obtain a 94% ee of remaining substrate. Either enantiomer could be recovered depending on the configuration of the tartrate ester employed. The complex used was prepared from titanium tetraisopropoxide, diisopropyl tartrate, and water as described by Kagan in his chiral sulfoxidation work.[1] Since many different sulfides are good substrates for this oxidation,[2] we proceeded to explore the substrate specificity of the kinetic resolution of analogues of compound **1**.

Examination of the structure of sulfide **1** reveals two additional heteroatom functional groups, the phenol and the amide. We sought to determine the influence of each of these on the outcome of the

* Corresponding author. Email: Panetta_Jill_A@Lilly.com

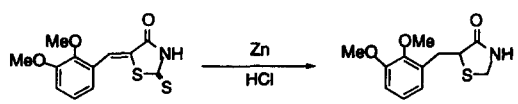
Table 1. Enantiomeric excess of recovered sulfides

Entry		% Reaction Completion[a]	%ee (NMR)	% ee (HPLC)
1		60	65	67
2		61	...[b]	62
3		57	45	47
4		53	0	...[b]
5		67	34	...[b]
6		59	7	7

[a] Based on isolated yields of starting material and products.

[b] Conditions to separate signals of individual enantiomers not found with this method.

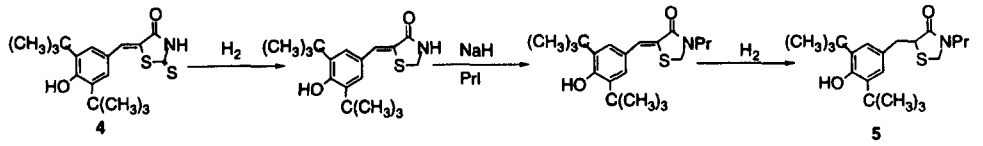
kinetic resolution. It is unlikely that the phenol could participate in coordination with the large titanium complex due to the bulky *tert*-Bu groups flanking it. However, to address the contribution of the phenol, the kinetic resolution was attempted on (±)5-[(2,3-dimethoxyphenyl)methyl]-4-thiazolidinone (**3**), synthesized as shown in Scheme 2. The resolution of this analogue was successful (see Table 1, entry 2), suggesting that the phenol is not a primary contributor to the interaction between compound **1** and the chiral complex.



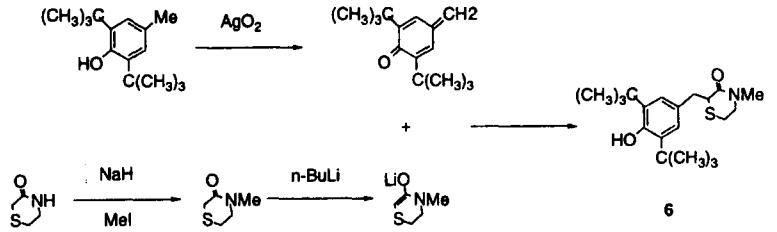
2 **3**

Scheme 2.

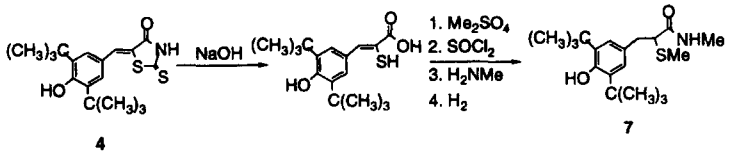
Four analogues of compound **1** were prepared in order to explore the importance of the amide functionality. The N-Pr derivative, **5**, the six-membered ring homologue, **6**, and the ring opened analogue, **7**, were synthesized as shown in Schemes 3–5, respectively.



Scheme 3.



Scheme 4.



Scheme 5.

The N-Me derivative, **8**, was prepared by Me iodide alkylation of **1**. Kinetic resolution of the N-Me analogue did occur but not to the extent of the unsubstituted compound (see Table 1, entries 1 and 3). The N-Pr derivative was not resolved at all under the same conditions (entry 4). A drop in the enantiomeric excess of the recovered sulfide was noted when the size of the lactam ring was expanded from a five to a six-membered ring (entries 3 and 5). Attempted resolution of an analogue in which the thiazolidinone ring was opened was unsuccessful (entry 6).

These experiments have shown that the success of the enantioselective oxidation of this sulfide by *tert*-Bu hydroperoxide is greatly influenced by the nature of the neighboring amide functionality. The interaction between the amide and the catalyst may be either steric or electronic.

Experimental section

General methods

3-Thiomorpholinone, **1**, **2**, and **4** were prepared by published procedures.[6,3a,7,8] Most of the general experimental methods have been published previously.[3a] In addition, THF was distilled from sodium/benzophenone and DMF was dried over molecular sieves. The n-BuLi in hexane was obtained from Aldrich and titrated.

Determination of enantiomeric excess

Two methods were used to determine the ee of the resolved products. HPLC on Chiracel columns using 280-nm detection resulted in enantiomer separation for **1**, **3**, **7**, and **8**. NMR spectroscopy of a $CDCl_3$ solution treated with the chiral shift reagent trifluoroanthranylethanol gave enantioselective shifting of signals in **1**, **5**, **6**, **7**, and **8**. Good agreement of these two methods was seen (see Table 1).

Kinetic resolution

The procedure given below for compound **1** was used for the kinetic resolution of all the substrates.

(-)5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-4-thiazolidinone (−)1

To a stirred suspension of 4 Å molecular sieves (1.05 g) in CH_2Cl_2 (25 mL) was added titanium tetraisopropoxide (0.45 mL, 1.5 mmol), (+)diisopropyl tartrate (0.63 mL, 3.0 mmol), and deionized water (27 μL, 1.5 mmol), respectively. The suspension was allowed to stir at rt for 20 min before addition of thiazolidinone (±)**1**[3a] (0.80 g, 2.5 mmol). After dissolution of the sulfide, the reaction was cooled to −20°C and 2.57 M *tert*-Bu hydroperoxide solution in isooctane (0.58 mL, 1.5 mmol) was added. The reaction was stirred at −20°C for 6 h, at which time the molecular sieves were removed by filtration. The filtrate was quenched by pouring into a stirred 50 mL solution prepared from citric acid monohydrate (3.3 g), ferrous sulfate heptahydrate (9.9 g), and deionized water. Stirring was continued for 30 min, then the layers were left to separate. The aqueous layer was extracted with an equal volume of CH_2Cl_2. The original CH_2Cl_2 layer and the CH_2Cl_2 extract were combined and dried (Na_2SO_4). Evaporation of the solvent followed by NMR analysis of a $CDCl_3$ solution of the residue showed a 40/60 ratio of **1** to its sulfoxide products (80/20 mixture of diastereomers). The evaporation residue was chromatographed on silica gel. Elution with 6 L of a 10%–50% Et acetate in hexane gradient yielded (−)**1** (0.29 g, 36% recovery) as a white foam: $[\alpha]^{20}_D$=−56.99 (c 1.0, MeOH); ee 67% (HPLC); Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 67.31; H, 8.55; N, 4.12.

When the reaction was taken to 70% completion using (−)diisopropyl tartrate (+)**1** was recovered as a white foam: $[\alpha]^{20}_D$=+70.41 (c 1.0, MeOH); ee 84% (HPLC); Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36. Found: C, 66.95; H, 8.22; N, 4.26.

5-[(2,3-Dimethoxyphenyl)methyl]-4-thiazolidinone 3

A stirred suspension of **2**[7] (38.0 g, 135 mmol) in a mixture of EtOH (1 L) and concd HCl (270 mL) was heated to 70°C. Zn dust (28.5 g) was added portionwise over 5 min. The reaction was refluxed for 30 min at which time more Zn dust (28.5 g) was added. After an addtional 30 min of reflux, concd HCl (270 mL) was added. Thirty min later the reaction was diluted with H_2O (2 L) and allowed to cool to rt. The supernatant was decanted from the resulting mixture and evaporated to approx. 1500 mL. Extraction with Et acetate, evaporation, and crystallization of the residue from Et acetate/hexane gave **3** (9.63 g, 28.4%): ^{1}H NMR ($CDCl_3$) δ 7.02 (dd, *J*=8, 8 Hz, 1H), 6.86 (m, 2H), 6.62 (s, 1H), 4.31 (d, *J*=6 Hz, 1H), 4.22 (d, *J*=6 Hz, 1H), 4.14 (dd, *J*=4, 10 Hz, 1H), 3.88 (s, 6H), 3.61 (dd, *J*=4, 14 Hz, 1H), 2.91 (dd, *J*=10, 14 Hz, 1H); FD MS 253 (M^+); Anal. Calcd for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.91; H, 5.82; N, 5.40.

Kinetic resolution of **3** as described above for compound **1** yielded (−)**3** (0.20 g, 32%) as a white foam: ee 62% (HPLC).

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-3-propyl-4-thiazolidinone 5

Hydrogenation of **4** (69.9 g, 200 mmol) in EtOH (4 L) in the presence of 5% Pd/C (200 g) under 500 psi of H_2 for 20 h at 100°C gave, after filtration and evaporation of solvent, the intermediate benzylidene thiazolidinone. This intermediate was chromatographed on silica gel eluting with 30% Et acetate in hexane and crystallized from Et acetate/hexane to yield 14.59 g (22.8%): ^{1}H NMR ($CDCl_3$) δ 7.71 (s, 1H), 7.45 (s, 1H), 7.43 (s, 2H), 5.47 (s, 1H), 4.66 (s, 2H), 1.49 (s, 18H). To a stirred solution of the benzylidene thiazolidinone (6.25 g, 19.6 mmol) in THF (196 mL) was added 60% NaH dispersion (0.78 g, 19.6 mmol) followed by Pr iodide (1.91 mL, 196 mmol). The reaction was heated to reflux for 2 d, then diluted with ether and water. The pH was adjusted to 2 with 1 N HCl while stirring. The organic layer was extracted with $NaHCO_3$ solution and brine, dried ($NaSO_4$), and chromatographed on silica gel. Elution with 8 L of a 5%–20% Et acetate in hexane gradient, then crystallization from Et acetate/hexane yielded the N-Pr-benzylidene thiazolidinone intermediate (4.47 g, 42%): ^{1}H NMR ($CDCl_3$) δ 7.48 (s, 1H), 7.42 (s, 2H), 5.43 (s, 1H), 4.60 (s, 2H), 3.55 (t, *J*=8 Hz,

2H), 1.69 (m, 2H), 1.49 (s, 18H), 0.99 (t, *J*=8 Hz, 3H). Hydrogenation of the N-Pr intermediate (7.00 g, 19.3 mmol) in THF (580 mL) in the presence of 5% Pd/C (28 g) under 60 psi of H_2 for 20 h at 60°C gave, after filtration and evaporation of the solvent, crude **5**. Crystallization from ether/hexane yielded pure **5** (3.79 g, 54%): ^{1}H NMR ($CDCl_3$) δ 7.08 (s, 2H), 5.10 (s, 1H), 4.16 (d, *J*=7 Hz, 1H), 4.00 (m, 1H), 3.93 (dd, *J*=2, 7 Hz 1H), 3.24 (m, 3H), 2.94 (dd, *J*=9, 14 Hz, 1H), 1.47 (m, 2H), 1.42 (s, 18H), 0.86 (t, *J*=7 Hz, 3H); FD MS 363 (M^+); Anal. Calcd for $C_{21}H_{33}NO_2S$: C, 69.38; H, 9.15; N, 3.85. Found: C, 69.34; H, 9.34; N, 3.78.

Attempted kinetic resolution of **5** as described for compound **1** yielded racemic **5** (0.41 g, 45%): ee 0% (NMR).

2-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-4-methyl-3-thiomorpholinone ***6***

To a stirred solution of 3-thiomorpholinone[6] (3.38 g, 28.8 mmol) in THF (288 mL) was added 60% NaH dispersion (1.27 g, 31.7 mmol) followed by Me iodide (1.80 mL, 28.8 mmol). After stirring for 2 h, the reaction was quenched with water and concentrated *in vacuo*. The resulting aqueous suspension was diluted with dichloromethane and acidified with 1 N HCl. Drying ($NaSO_4$) and evaporation of the dichloromethane layer gave a solid which was chromatographed on silica gel. Elution with 6 L of a 10%–50% acetone in hexane gradient yielded 4-Me-3-thiomorpholinone (3.02 g, 80%): ^{1}H NMR ($CDCl_3$) δ 3.65 (t, *J*=6 Hz, 2H), 3.35 (s, 2H), 3.05 (s, 3H), 2.9 (t, *J*=6 Hz, 2H). 4-Me-3-thiomorpholinone (1.88 g, 14.3 mmol) dissolved in THF (72 mL) was cooled to 0°C and treated with 1.37 M n-BuLi in hexane (20.9 mL, 28.7 mmol). After 5 min the cold bath was removed. Ten min later a solution of 2,6-di-*tert*-Bu-quinone methide, prepared by adding Ag_2O (33.2 g, 143 mmol) to 2,6-di-*tert*-Bu-4-Me-phenol (BHT) (3.16 g, 14.3 mmol) in THF (72 mL) stirring for 30 min and filtering, was added dropwise over 20 min. The reaction was stirred 3 h, quenched with 1 N HCl, and evaporated to an aqueous suspension. The crude product was extracted into Et acetate, dried ($NaSO_4$) and concentrated *in vacuo*. Chromatography on silica gel eluting with 8 L of a 0–50% Et acetate in hexane gradient yielded **6** (2.0 g, 40%): ^{1}H NMR ($CDCl_3$) δ 7.1 (s, 2H), 5.15 (s, 1H), 3.7–3.4 (m, 4H), 3.1 (s, 3 H), 2.85 (dd, *J*=9, 15 Hz, 1H), 2.75 (t, *J*=6 Hz, 2H), 1.45 (s, 18H); FD MS 349 (M^+); Anal. Calcd for $C_{20}H_{31}NO_2S$: C, 68.72; H, 8.94; N, 4.01. Found: C, 68.95; H, 8.92; N, 4.23.

Kinetic resolution of **6** as described above for compound **1** yielded (−)**6** (0.26 g, 29%): ee 34% (NMR).

3,5-Bis(1,1-dimethylethyl)-4-hydroxy-N-methyl-α-(methylthio)-benzenepropanamide ***7***

To a stirred suspension of **4**[8] (160.3 g, 458.7 mmol) in water (917 mL) was added 5 N NaOH (459 mL, 2.29 mol). The reaction was refluxed 1 h, cooled to rt and extracted thoroughly with CH_2Cl_2. The aqueous layer was acidified with 2.5 L 1 N HCl. The precipitated solid was collected and redissolved in CH_2Cl_2. Washing with water, drying ($NaSO_4$) and evaporation gave the α-mercaptocinnamic acid intermediate (119.6 g, 78.9%) which was used without further purification. To a solution of this intermediate in DMF (1.6 L) was added potassium carbonate (67.0 g, 485 mmol) and Me sulfate (36.7 mL, 388 mmol). The reaction was stirred 20 min and acidified carefully with 1 N HCl. The precipitated solid was collected and redissolved in Et acetate. The Et acetate solution was washed with water, dried ($NaSO_4$), and concentrated *in vacuo*. Chromatography on silica gel, eluting with 8 L of a 10%–40% Et acetate in hexane gradient, yielded the α-methylmercaptocinnamic acid intermediate (47.7 g, 38%) which was used without further purification. To a solution of this intermediate (40.6 g, 126 mmol) in THF (630 mL) was added thionyl chloride (9.17 mL, 126 mmol). The resulting solution was stirred 1 h and then added to 40% aqueous methylamine (976 mL) in THF (630 mL). After stirring 25 min the reaction was concentrated *in vacuo*, then redissolved in Et acetate and water. The pH was adjusted to 7 with concd HCl. The organic phase was dried ($NaSO_4$) and concentrated. Chromatography on silica gel eluting with 8 L of a 10%–50% Et acetate in hexane gradient gave the N-Me, α-methylmercaptocinnamamide intermediate (17.2 g, 40.8%): ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.9 (s, 2H), 7.5 (m, 1H), 5.55 (s, 1H), 3.0 (d, *J*=6 Hz, 3H), 2.25 (s, 3H), 1.45 (s, 18H).

Hydrogenation in THF (1.5L) in the presence of 5% Pd/C (86 g) under 60 psi of H_2 for 20 h at 60°C yielded, after filtration and evaporation of solvent, crude **7**. Crystallization from Et acetate/hexane resulted in pure **7** (10.3 g, 59.4%): ^{1}H NMR ($CDCl_3$) δ 7.0 (s, 2H), 6.5 (s, 1H), 5.1 (s, 1H), 3.4 (dd, *J*=8, 8 Hz, 1H), 3.2 (dd, *J*=8, 17 Hz, 1H), 2.9 (dd, *J*=8, 17 Hz, 1 H), 2.8 (d, *J*=6 Hz, 3H), 2.1 (s, 3H), 1.45 (s, 18H); FD MS 337 (M^+); Anal. Calcd for $C_{19}H_{31}NO_2S$: C, 67.61; H, 9.26; N, 4.15. Found: C, 67.69; H, 9.22; N, 4.23.

Attemped kinetic resolution of **7** as described for compound **1** yielded (−)**7** (0.34 g, 40%): ee 7% (HPLC), 7% (NMR).

5-[[3,5-Bis(1,1-dimethylethyl)-4-hydroxyphenyl]methyl]-3-methyl-4-thiazolidinone 8

To a stirred solution of **1** (6.43 g, 20 mmol) in THF (100 mL) was added 60% NaH dispersion (0.88 g, 22 mmol) followed by Me iodide (1.25 mL, 20 mmol). After stirring for 23 h, the reaction was diluted with ether and 1 N HCl. Drying ($NaSO_4$) and evaporation of the ether layer resulted in an orange foam which was chromatographed on silica gel. Elution with 8 L of a 10%–30% Et acetate in hexane gradient, then crystallization from ether/hexane yielded **8** (3.98 g, 59.3%): ^{1}H NMR ($CDCl_3$) δ 7.1 (s, 1H), 5.1 (s, 1H), 4.1 (d, *J*=6 Hz, 1H), 3.95 (dd, *J*=3, 9 Hz, 1H), 3.85 (d, *J*=6 Hz, 1H), 3.25 (dd, *J*=3, 15 Hz, 1H), 2.95 (dd, *J*=9, 15 Hz, 1H), 2.9 (s, 3H), 1.45 (s, 18H); FD MS 335 (M^+); Anal. Calcd for $C_{19}H_{29}NO_2S$: C, 68.02; H, 8.71; N, 4.17. Found: C, 68.22; H, 8.80; N, 4.21.

Kinetic resolution of **8** as described above for compound **1** yielded (−)**8** (0.35 g, 42%): ee 47% (HPLC), 45% (NMR).

References

1. Pitchen, P.; Duñach, E.; Deshmukh, M. N.; Kagan, H. B. *J. Am. Chem. Soc.* **1984**, *106*, 8188–8193.
2. (a) Brunel, J. M.; Kagan, H. B. *Bull. Soc. Chim. Fr.* **1996,** *133,* 1109–1115; (b) Di Furia, F.; Licini, G.; Modena, G.; Motterle, R. *J. Org. Chem.* **1996**, *61,* 5175–5177; (c) Scettri, A.; Bonadies, F.; Lattanzi, A. *Tetrahedron: Asymmetry* **1996,** *7,* 629–632; (d) Brunel, J. M.; Diter, P.; Duetsch, M.; Kagan, H. B. *J. Org. Chem.* **1995,** *60,* 8086–8088; (e) Kagan, H. B.; Rebiere, F. *Synlett* **1990**, 643–650 and references cited therein.
3. (a) Phillips, M. L.; Berry, D. M.; Panetta, J. A. *J. Org. Chem.* **1992**, *57*, 4047–4049; (b) Nemecek, C.; Kagan, H. B. *Polish J. Chem.* **1994**, *68*, 2467–2475; (c) Griffiths, S. L.; Perrio, S., Thomas, S. E. *Tetrahedron: Asymmetry* **1994,** *5,* 1847–1864.
4. (a) Scettri, A.; Bonadies, F.; Lattanzi, A.; Senatore, A.; Soriente, A. *Tetrahedron: Asymmetry* **1996**, *7*, 657–658; (b) Komatsu, N.; Hashizume, M.; Sugita, T.; Uemura, S. *J. Org. Chem.* **1993**, *58*, 7624–7626.
5. Allbee, W. H.; Jacobs, J.; Phillips, M.; Fisher, L.; Panetta, J.; Gidda, J. S. *Gastroenterology* **1991**, *100*, A556.
6. Matarese, R. M.; Pecci, L.; Ricci, G.; Cavallini, D. *J. Chromatogr.* **1984**, *294*, 413–418.
7. Barltrop, J. A. *J. Chem. Soc.* **1946**, 958–965.
8. Teuber, H.-J.; Krause, H.; Berariu, V. *Liebigs Ann. Chem.* **1978**, 757–770.

(Received in USA 28 March 1997; accepted 30 April 1997)