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MECHANISTIC STUDIES ON RACEMIZATION OF CHIRAL 2-ARYLTHIAZOLIDINONES

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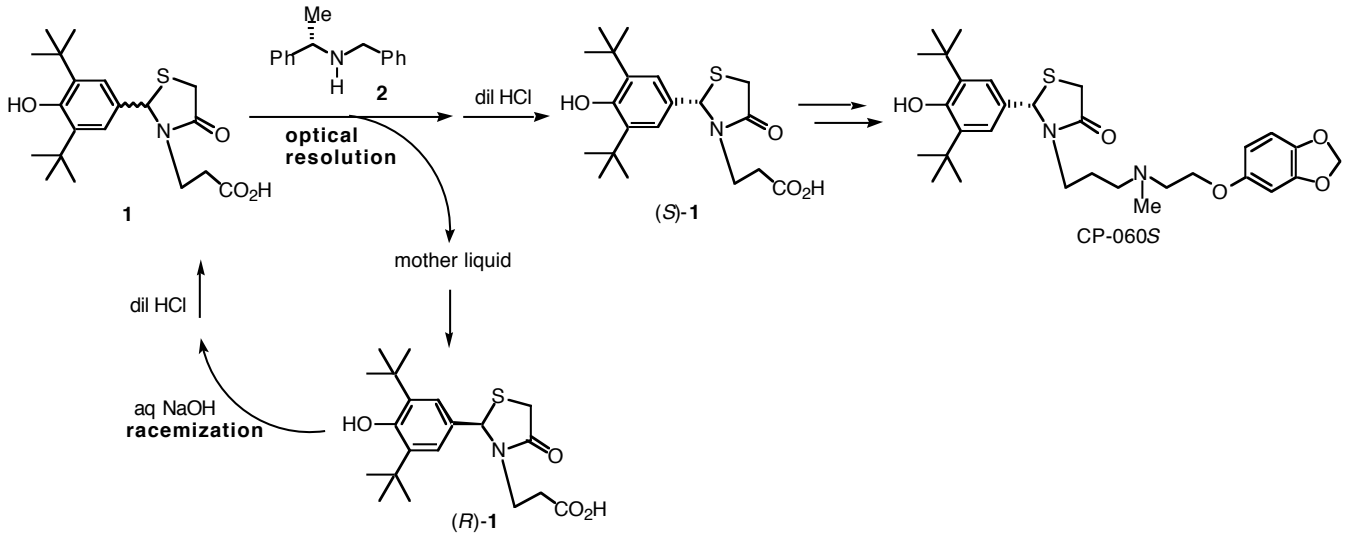
Abstract - Mechanistic studies on racemization of chiral 3-[(2*S*)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-4-oxo-1,3-thiazolidin-3-yl]propanoic acid is described. This racemization is triggered by deprotonation of phenolic hydroxyl group. We propose that the racemization proceeds *via* a novel mechanism involving ring opening-closure equilibrium of the thiazolidinone ring.

In the course of our recent studies on a novel cardioprotective drug, we found (*S*)-(–)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-(3,4-methylenedioxyphenoxy)ethyl]amino]propyl]-1,3-thiazolidin-4-one (CP-060*S*) possessed not only potent Ca^{2+} antagonistic activity but Ca^{2+} overload inhibition and antioxidant activities as well. [1, 2] We previously reported a practical synthetic method for this compound [3] in which racemic carboxylic acid intermediate (**1**) was optically resolved by selective crystallization from a mixture of diastereomeric salts with chiral amine (**2**). Furthermore, recycling *via* racemization of the mixture rich in undesired (*R*)-**1**, obtained from the mother liquid in the resolving process, resulted in remarkable improvement of the conversion yield as shown in Scheme 1.

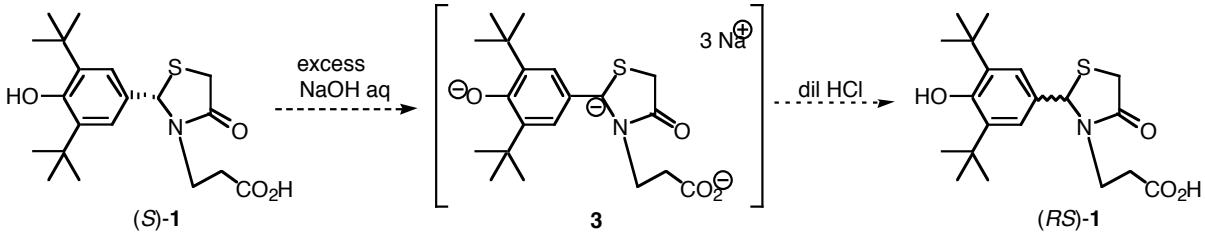
Scheme 1. Synthetic Route of CP-060*S* *via* Optical Resolution and Racemization Cycle



As far as we know, there is no other report about racemization of chiral 2-arylthiazolidinones. In this paper we describe mechanistic studies on the racemization.

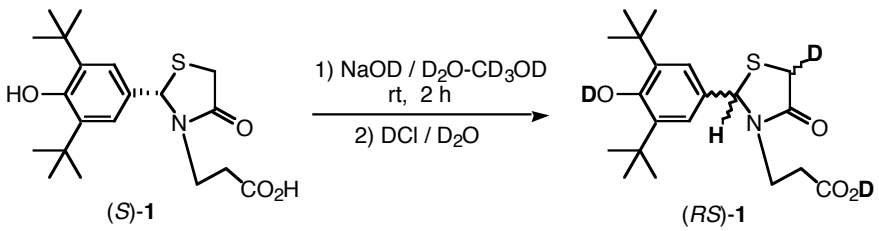
This racemization proceeds under basic conditions such as treatment with aqueous NaOH solution at room temperature. We simply presumed that the racemization proceeded by deprotonation of the 2-position, which is adjacent to the S, N, and aromatic ring and whose proton is supposedly acidic as shown in Scheme 2.

Scheme 2. Initial Speculation of Racemization Mechanism



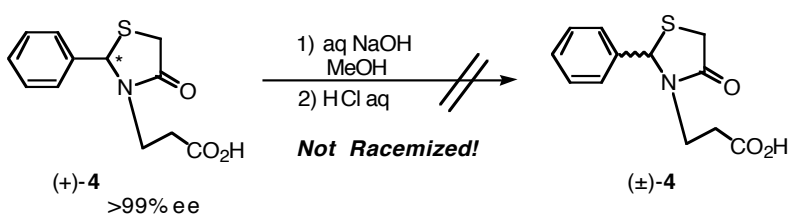
In order to clarify the mechanism, a deuteration study was tried. Thus optically active (*S*)-**1** was treated with 10 equivalent of NaOD solution, followed by treatment with DCl to give racemic mixture of deuterated **1**. ^{1}H-NMR spectrum of the deuterated **1** showed that carboxylic and phenolic hydrogens and a hydrogen at the 5-position were deuterated, however, the hydrogen at the 2-position was not deuterated at all. This result suggests that the racemization proceeded in different fashion.

Scheme 3. Deuteration Study in Racemization of (*S*)-**1**



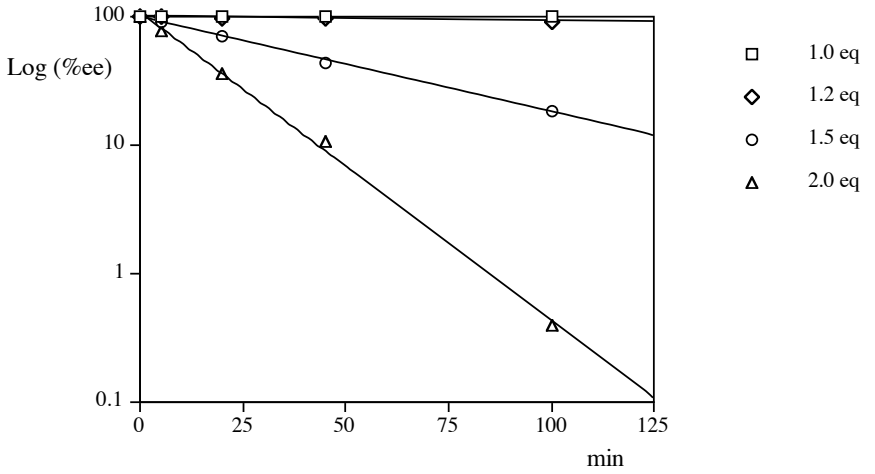
In parallel, racemization with several different amounts of base was tried. Though the racemization of (*S*)-**1** did not occur with 1.0 equivalent of NaOH, 1.2 equivalent of the base brought about slight racemization. Since the racemization occurred by treatment with more than 1 equivalent of NaOH, the deprotonation of phenolic hydroxyl group must be a trigger of the racemization. This was supported by observation that racemization of (+)-**4**, which does not have phenolic hydroxyl group, did not proceeded at all even with 10 equivalent of NaOH.

Scheme 4.



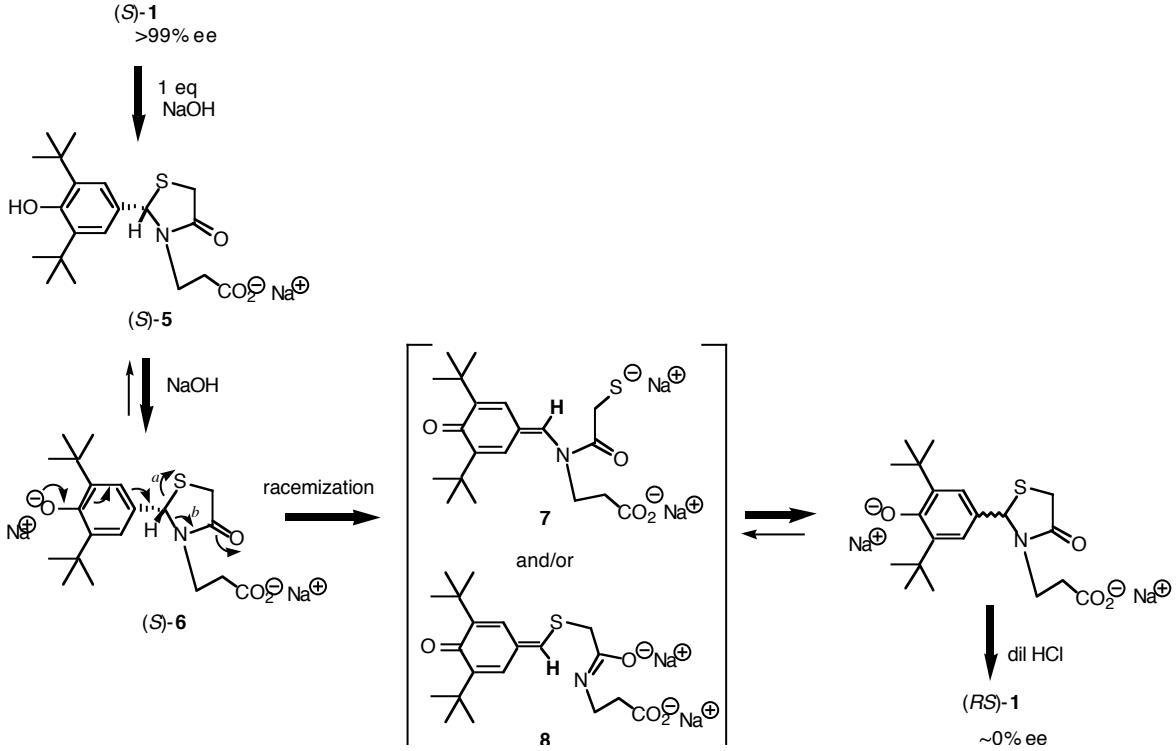
As for the kinetics for the racemization of (*S*)-**1**, the rates for racemization in each concentration of NaOH showed good linear relationships with first-order rate plots as shown in Figure 1, and the time for 50% racemization were 13.1, 0.68, and 0.23 h when 1.2, 1.5, and 2.0 equivalent of NaOH were used, respectively.

Figure 1. Racemization Rates of (*S*)-**1** with 1.0 ~ 2.0 eq of NaOH



This racemization should be consider to separate into following steps as shown in Scheme 5. Treatment of 1 equivalent of NaOH generates monoanion ((*S*)-**5**). Further addition of the base generates chiral dianion ((*S*)-**6**) in which equilibrium lies so far to (*S*)-**6** because of acidity of phenolic hydroxyl hydrogen. It is indicated from the racemization rates as shown in Figure 1 that the racemization is first-order kinetics in concentration of the dianion ((*S*)-**6**), and also that the racemization proceeds by intramolecular fashion.

Scheme 5. A Novel Mechanism *via* Thiazolidinone Ring Opening-Closure Equilibrium



From these considerations, we propose that the racemization mechanism is based on thiazolidinone ring opening-closure equilibrium. There are two possible ways in the ring opening: one is C–S bond cleavage (*pass a*) to give thiolate anion (**7**) and the other is C–N bond cleavage (*pass b*) to give imidate anion (**8**). In order to clarify the pass-way of the racemization, the racemization reaction was monitored by NMR. However, neither the ring opened intermediate (**7**) or (**8**) was observed. This suggested that the equilibrium lied so far to the ring closure form. Considering pKa values of the corresponding conjugate acids of the ring-opening intermediates, [4] the pKa value of the thiol hydrogen (pKa=10~11) is reportedly similar to that of the phenolic hydroxyl hydrogen (pKa=8~11). On the other hand, the pKa value of amide hydrogen (pKa=~17) is much bigger than that of phenolic hydroxyl and even higher than that of water (pKa=15.7). Based on these facts, we speculate that the racemization proceeded most likely *via* thiolate anion intermediate (**7**).

EXPERIMENTAL

General: The melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. ^{1}H-NMR spectra were measured with a Varian Mercury-300 spectrometer (300 MHz) with tetramethylsilane as the internal standard. IR spectra were recorded on a Hitachi Model 270-3 infrared spectrophotometer. EI MS spectra were determined on a Shimadzu GCMS-QP1000 instrument. Optical rotations were determined on a Horiba SEPA-200 high sensitive polarimeter. Analytical and preparative HPLC were performed using Shimadzu LC-6AD pumps, a Shimadzu SPD-10A UV-detector operated at 280 nm. The chiral stationary phase columns, Chiralpak AD, were purchased from Daicel Chemical Industries.

Deuteration Study in Racemization of (*S*)-1

To a solution of (*S*)-**1** (76 mg, 0.2 mmol, >99% ee) in CD_3OD (2 mL) was added 40% NaOD in D_2O solution (205 mg, 2.0 mmol) under a nitrogen atmosphere. The solution was stirred for 2 h at rt, acidified with 18% DCl in D_2O solution, and extracted with AcOEt. The extract was dried over Na_2SO_4 and concentrated under reduced pressure to give 77 mg of racemic **1** (~ 0%ee) as a crude product. The enantiomeric excess of **1** was determined by chiral HPLC [column: Chiralpak AD; mobile phase: hexane/*i*-PrOH/TFA (85:15:0.2); flow rate: 0.5 mL/min]. The retention times were 7.4 and 9.3 min for the *R* and *S* enantiomers, respectively.

Kinetic Studies in Racemization of (*S*)-1

(*S*)-**1** (>99% ee, 76 mg, 0.2 mmol) was dissolved in methanol (2 mL) at 27 °C, followed by addition of aq NaOH (each 0.4 mL of 0.5 M, 0.6 M, 0.75 M, and 1.0 M aq NaOH for 1.0 eq, 1.2 eq, 1.5 eq, and 2.0 eq of NaOH, respectively) and each mixture was stirred at 27± 1 °C under a nitrogen atmosphere. A 100 μL aliquot was taken from the solution by a syringe at appropriate time intervals and acidified with 2 N aq HCl immediately. Each acidified sample was extracted with AcOEt and extracts were dried over

$MgSO_4$ and concentrated to give residue. The enantiomeric excess of each residue was analyzed by HPLC under the same condition as mentioned above.

Synthesis of racemic 4

To a suspension of powdered β-alanine (8.9 g, 100 mmol) in toluene (100 mL) were added NEt_3 (27.9 mL, 200 mmol) and TMSCl (25.4 mL, 200 mmol) at 50 ℃, and the mixture was stirred for 1 h at the same temperature. Benzaldehyde (5.3 g, 50 mmol) was added to the reaction mixture, and the mixture was stirred for 1 h at 80 ℃ and then α-mercaptoacetic acid (6.94 mL, 100 mmol) was added dropwise to the solution. After stirring for 3 h at 80 ℃, the reaction mixture was poured into water and extracted with AcOEt. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by chromatography on silica gel with $CHCl_3$/MeOH (98:2), followed by recrystallization from $CHCl_3$/hexane to give 7.76 g (62%) of **4** as colorless crystals: mp 122–124 ℃; IR (KBr) 3060, 1750, 1656, 1414, 1180, 1150, 770, 698 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.43 (1H, ddd, *J* = 16.8, 6.9, 6.0 Hz), 2.70 (1H, dt, *J* = 16.8, 7.2 Hz), 3.12 (1H, dt, *J* = 14.4, 7.2 Hz), 3.6-3.8 (1H, m), 3.71 (1H, d, *J* = 15.9 Hz), 3.82 (1H, dd, *J* = 15.9, 1.5 Hz), 5.73 (1H, d, *J* = 1.5 Hz), 7.3-7.5 (5H, m), 10.10 (1H, br s); MS *m/z* 251 (M^+), 178. Anal. Calcd for $C_{12}H_{13}NO_3S$: C, 57.35; H, 5.21; N, 5.57; S, 12.76. Found: C, 57.07; H, 5.16; N, 5.31; S, 12.64.

Optical Resolution of Racemic 4 by Using Preparative HPLC

4 (1 g) was dissolved in hot ^{i}PrOH/AcOEt (9:1, 10 mL) and injected in 0.4 mL aliquots into a preparative HPLC with a chiral column [column: Chiralpak AD (ϕ 2 × 25 cm); mobile phase: hexane/*i*-PrOH/TFA (80:20:0.2); flow rate: 10 mL/min]. Two pools of material were isolated with retention times of 14.1 min ((+)-**4** as an oil; 425 mg, >99% ee, $[\alpha]_D$ = +47.4° (c = 0.794, $CHCl_3$)) and 16.5 min ((–)-**4** as an oil; 405 mg, >99% ee, $[\alpha]_D$ = –46.1° (c = 0.794, $CHCl_3$)). The ^{1}H-NMR spectra of (+)-**4** and (–)-**4** are the same as that of racemic **4**.

Treatment of (+)-4 with Excess NaOH

To a solution of (+)-**4** (50 mg, 0.2 mmol, >99% ee) in MeOH (2 mL) was added 5.0 M aq NaOH (0.4 mL, 2.0 mmol) under a nitrogen atmosphere. After the mixture stirred for 2 h at rt, the mixture was acidified with 2 N aq HCl and extracted with AcOEt. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to recover 48 mg of optically active (+)-**4** (>99% ee).

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