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TETRAHEDRON: *ASYMMETRY*

Improved synthetic methods of CP-060*S*, a novel cardioprotective drug

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Abstract

Two synthetic methods of CP-060*S*, (−)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-[3-[*N*-methyl-*N*-[2-[3,4-(methylenedioxy)phenoxy]ethyl]amino]propyl]-1,3-thiazolidin-4-one (−)-**1**, have been developed. The first method involved preparative HPLC resolution of bromo-intermediate **4**. The second one involved resolution of **1** by crystallization of the corresponding diastereomeric salt.

1. Introduction

In the course of our recent studies on a novel cardioprotective drug, we found that 2-aryl-3-aminoalkyl-1,3-thiazolidin-4-one derivative **1** possessed not only potent Ca^{2+} antagonistic activity but also Ca^{2+} overload inhibition and antioxidant activity.[1] In in vitro studies, the Ca^{2+} antagonistic activity of the (*S*)-enantiomer (−)-**1** (CP-060*S*) was about 10 times more potent than that of the (*R*)-enantiomer (+)-**1**, though both enantiomers had similar potency in Ca^{2+} overload inhibition and antioxidant activity.[2] As for the synthesis of chiral 2-arylthiazolidinones, there is no report of a successful enantioselective method, except for 5-substituted derivatives.[3,4] We previously performed a resolution of **1** using preparative HPLC; however, a maximum of only 5 mg of racemic **1** was resolved in a single run.[2] In order to supply enough (−)-**1** for pharmacological and toxicological evaluations, an efficient synthetic method for (−)-**1** was required. We report here two improved resolution methods. The first one describes HPLC resolution of **1** and its synthetic intermediates **2**–**4** using chiral columns.[5] The second one describes the resolution of **1** by crystallization of its salt with (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate.[6]

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2. Results and discussion

2.1. HPLC resolution of **1** and synthetic intermediates **2–4** using chiral columns

Initially, we focused our efforts on HPLC resolution of **1** using various commercially available chiral columns. We found that Chiralcel OD and Chiralpak AS were effective for the separation as shown in Fig. 1. Interestingly, a reversal of elution order was observed between Chiralcel OD and Chiralpak AS. In both cases, enantiomers of **1** were completely resolved, and the resolution factors (*R*s) of 2.5 and 1.4 were obtained, respectively, as shown in Table 1. However, as mentioned before, a maximum of only 5 mg (9.2 μmol) of racemic **1** was resolved in a single run using preparative Chiralcel OD (Ø 2×25 cm).[2] Therefore, we sought another compound which could be resolved more effectively.

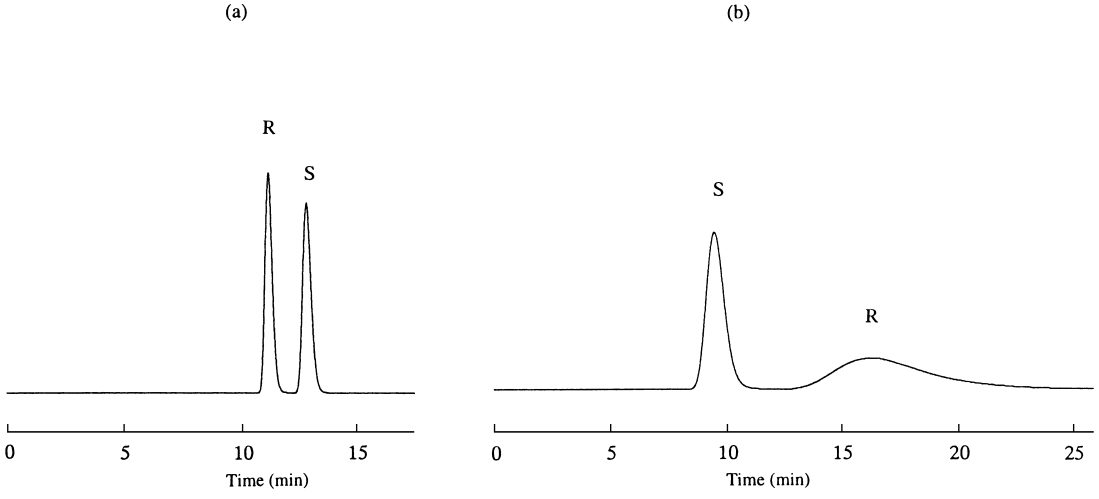
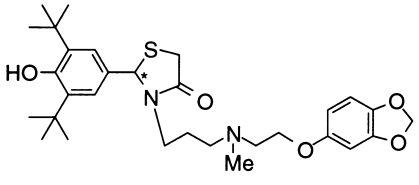


Figure 1. Analytical HPLC resolution of **1** using Chiralcel OD (a), and Chiralpak AS (b). Eluent: (a) hexane:^{i}PrOH (80:20), 0.7 ml/min; (b) hexane:^{i}PrOH:Et_2NH (40:60:0.3), 0.7 ml/min

Table 1
HPLC resolution of **1**

chiral column	k'_1	k'_2	α	*R*s
Chiralcel OD	1.56	1.93	1.24	2.5
Chiralpak AS	1.17	2.7	2.31	1.4



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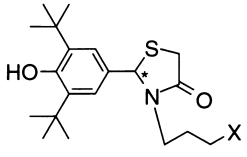


2 ; X = OH
3 ; X = Cl
4 ; X = Br

We presumed that the low resolution efficiency of **1** was because of the basicity or polarity of the tertiary amine and/or the flexibility of the side chain including the aryloxyethylamino moiety. Considering this matter, the synthetic intermediates **2–4**, which do not have the tertiary amine or the

long flexible side chain, were then investigated under the same conditions as for **1** using Chiralcel OD. The results are summarized in Fig. 2 and Table 2. Halides **3** and **4** showed better resolution as expected, though the resolution of alcohol **2** was lower than that of **1**. The best resolution was observed for bromide **4** with an *R*s value of 6.5, more than twice that of **1**.

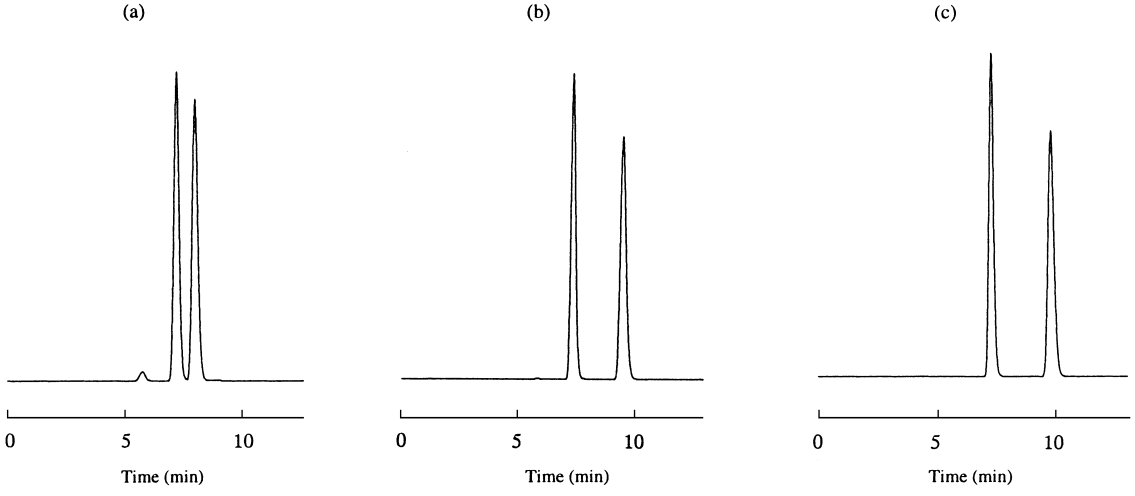
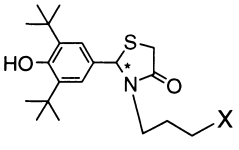


Figure 2. Analytical HPLC resolution of **2** (a), **3** (b), and **4** (c) using Chiralcel OD. Eluent: hexane:^{i}PrOH (80:20), 0.7 ml/min

Table 2
HPLC resolution of **2**–**4** using Chiralcel OD



compd	X	k'_1	k'_2	α	*R*s
2	OH	0.65	0.83	1.27	1.8
3	Cl	0.68	1.17	1.72	5.0
4	Br	0.68	1.25	1.85	6.5

When we performed the resolution of **4** using preparative Chiralcel OD (Ø 2×25 cm), 50 mg (117 μmol) of **4** was successfully resolved in a considerably shorter time as shown in Fig. 3b. Based on the molar ratio of separable amounts in a single run, the resolution efficiency of **4** was over 12 times higher than that of **1**.

Reaction of resolved (−)-**4** with amine **5** produced (−)-**1** as an oil, which was converted to the corresponding salt in 80% yield from (−)-**4** by treatment with fumaric acid. Finally, the enantiomerically pure fumarate (99.5% ee) was obtained by crystallization, although some racemization occurred during the amination step as can be seen from Scheme 1.

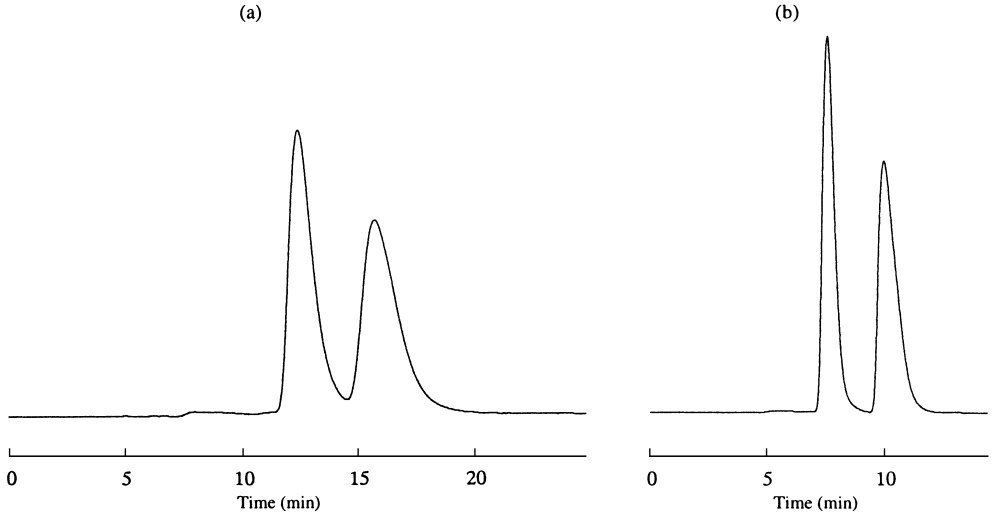
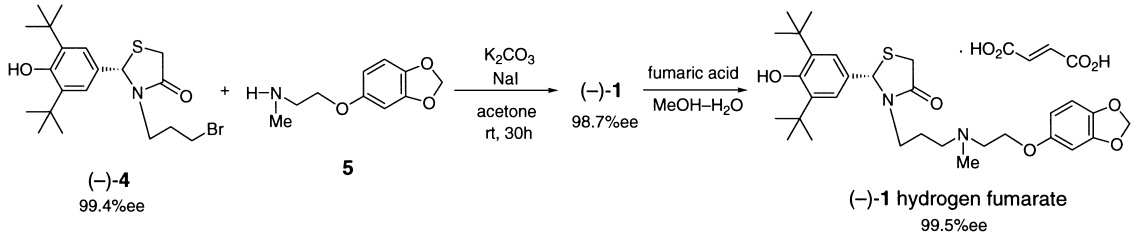


Figure 3. Preparative HPLC resolution of **1** (a) and **4** (b) using Chiralcel OD (Ø 2×25 cm). Eluent: hexane:^{i}PrOH (80:20), 13.5 ml/min. Injection: (a) 5 mg of **1**; (b) 50 mg of **4**



Scheme 1.

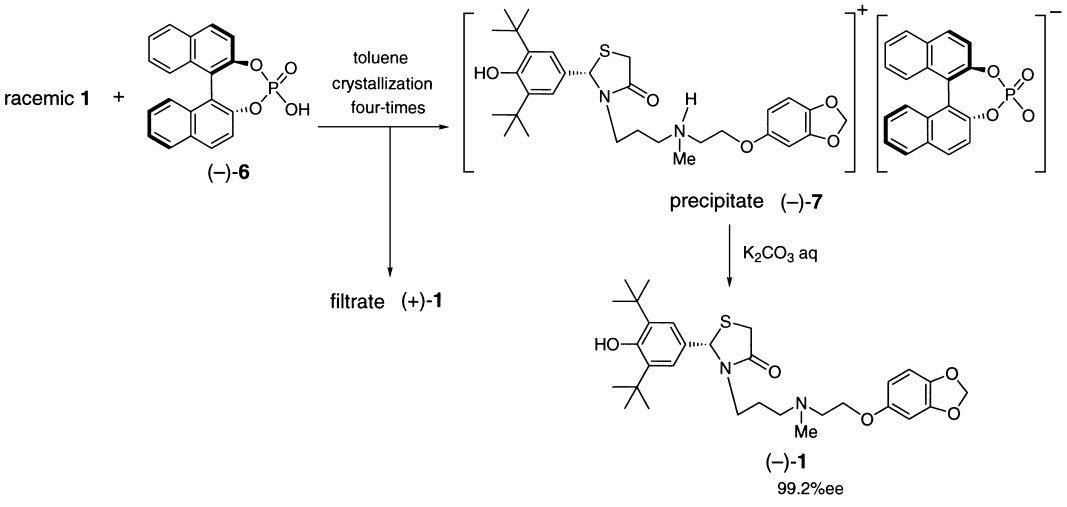
2.2. *Resolution of **1** by crystallization of its (R)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate salt*

In parallel with the above method, we also investigated the resolution of **1** for large scale supply via diastereomeric salt formation with chiral acids. Initially, we focused on the resolution of **1** using common reagents (1-camphor-10-sulphonic acid, mandelic acid, etc.) reported by Wilen,[7] but none of the salts crystallized. Then, we tried many possible chiral acids, and finally found that (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (−)-**6** was a suitable reagent for the resolution of **1** (Scheme 2). As a result, enantiomerically pure (−)-**1** (>99% ee) was obtained by four successive recrystallizations of its salt and subsequent treatment with 10% K_2CO_3 solution.

3. Experimental

3.1. *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. Optical rotations were determined on a Horiba SEPA-200 high sensitivity polarimeter. Analytical and preparative HPLC were performed using Shimadzu LC-6AD pumps and a Shimadzu SPD-10A UV-detector operated at 280 nm. The following chiral stationary



Scheme 2.

phase columns were employed for analytical (Ø 0.46×25 cm) and preparative separations (Ø 2×25 cm), and were purchased from Daicel Chemical Industries. Polysaccharide derivatives (cellulose tris(3,5-dimethylphenylcarbamate) for Chiralcel OD and amylose tris[(*S*)-1-phenylethylcarbamate] for Chiralpak AS) were coated on silica gel with particle size of 10 μm. The dead time (t_0) was estimated to be 4.4 min with 1,3,5-tri-*tert*-butylbenzene as a non-retained compound.[8] Capacity factors (k'_1, k'_2) were calculated by using $(t_1-t_0)/t_0$ and $(t_2-t_0)/t_0$, respectively. Separation factor (α) was calculated as k'_2/k'_1. Resolution factor (*R*s) was calculated as $2(t_2-t_1)/(W_1+W_2)$, where t_1 and t_2 are retention times and W_1 and W_2 are band widths of each enantiomer.

3.2. Syntheses of racemic thiazolidinones **1**–**4**

The racemic compounds **1**–**4** were prepared as reported earlier.[1,2]

3.3. Preparative HPLC resolution of bromide **4**

Bromide **4** (10 g) was dissolved in ^{i}PrOH:AcOEt (1:1) (80 ml) and injected in 0.4 ml aliquots into the preparative chiral column (Chiralcel OD, Ø 2×25 cm). The HPLC condition was as follows: eluent, hexane:^{i}PrOH (80:20); flow rate, 13.5 ml/min; detection wavelength, 280 nm. Two pools of material were isolated with retention times of 7.7 min ((+)-**4**: 4.6 g, 99.9% ee, mp 155–158°C, $[\alpha]_D$=31.1 (*c* 0.650, $CHCl_3$)) and 10.1 min ((−)-**4**: 4.5 g, 99.4% ee, mp 155–157°C, $[\alpha]_D$=−31.3 (*c* 0.624, $CHCl_3$)). The ^{1}H NMR spectra of (+)-**4** and (−)-**4** are the same as that of racemic **4**. ^{1}H NMR ($CDCl_3$): δ 1.44 (18H, s), 1.8–2.2 (2H, m), 2.9–3.1 (1H, m), 3.2–3.4 (2H, m), 3.4–3.6 (1H, m), 3.69 and 3.80 (2H, ABq, *J*=15.6 Hz), 5.35 (1H, br s), 5.58 (1H, s), 7.12 (2H, s).

3.4. Synthesis of (−)-**1** by amination of (−)-**4**

To a solution of (−)-**4** (3.67 g, 8.57 mmol, 99.4% ee) and *N*-methyl-*N*-[2-[3,4-(methylenedioxy)-phenoxy]ethyl]amine **5** (1.84 g, 9.44 mmol) in acetone (30 ml) was added K_2CO_3 (3.55 g, 25.7 mmol) and NaI (6.42 g, 42.9 mmol) under a nitrogen atmosphere, and the mixture was stirred for 30 h at room temperature. The reaction mixture was poured into water and extracted with AcOEt. The extract was

washed with 5% $Na_2S_2O_3$ solution, 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) to give 4.08 g (88%, 98.7% ee) of (−)-**1** as a colorless oil. Compound (−)-**1** was then treated with an equimolar amount of fumaric acid, and recrystallized from MeOH–H_2O to give 4.52 g (80%, 99.5% ee) of (−)-**1** hydrogen fumarate salt as colorless crystals. Mp 143–144°C; ^{1}H NMR (DMSO-d_6): δ 1.36 (18H, s), 1.5–1.8 (2H, m), 2.18 (3H, s), 2.3–2.5 (2H, m), 2.6–2.8 (3H, m), 3.3–3.5 (1H, m), 3.63 and 3.75 (2H, ABq, *J*=15.7 Hz), 3.95 (2H, t, *J*=5.6 Hz), 5.4 (3H, br s), 5.78 (1H, s), 5.94 (2H, s), 6.32 (1H, dd, *J*=8.3, 2.6 Hz), 6.58 (1H, d, *J*=2.6 Hz), 6.60 (2H, s), 6.77 (1H, d, *J*=8.3 Hz), 7.10 (2H, s); $[\alpha]_D$=−33.5 (*c* 1.071, EtOH).

*3.5. Optical resolution of **1** by diastereomeric salt formation*

A mixture of racemic **1** (10.8 g, 20 mmol) and (*R*)-(−)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate (−)-**6** (4.2 g, 12 mmol) in toluene (100 ml) was heated to boiling until all of the solid material dissolved. The mixture was cooled down and left overnight. The precipitate was then filtered, washed with toluene, and dried in vacuo to give 10.6 g of the corresponding salt (69% ee). This precipitate was recrystallized three times to give 4.4 g (25%, 99.2% ee) of (−)-**7**. Mp 194–197°C; ^{1}H NMR (CD_3OD): δ 1.41 (18H, s), 1.6–1.9 (2H, m), 2.80 (3H, s), 2.8–3.2 (3H, m), 3.3–3.5 (3H, m), 3.68 and 3.77 (2H, ABq, *J*=15.9 Hz), 4.18 (2H, t, *J*=5.3 Hz), 5.72 (1H, s), 5.90 (2H, s), 6.39 (1H, dd, *J*=8.2, 2.6 Hz), 6.57 (1H, d, *J*=2.6 Hz), 6.72 (1H, d, *J*=8.2 Hz), 7.17 (2H, s), 7.1–7.3 (4H, m), 7.3–7.5 (2H, m), 7.53 (2H, d, *J*=7.6 Hz), 7.95 (2H, d, *J*=7.6 Hz), 8.01 (2H, d, *J*=7.6 Hz); $[\alpha]_D$=−247.9 (*c* 0.236, MeOH). The above salt (−)-**7** was suspended in AcOEt and 10% K_2CO_3 solution was added. The mixture was stirred at room temperature and extracted with AcOEt, washed again with 10% K_2CO_3 solution, dried over Na_2SO_4, and concentrated under reduced pressure to give 2.2 g (20%, 99.2% ee) of (−)-**1** as a colorless oil.

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