Synthesis and Optical Resolution of an Antiallergic Agent KW4099 with Thromboxane A₂ Antagonistic Activity

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A new antiallergic agent with thromboxane A₂ antagonistic activity, KW4099, was synthesized by a simple method. Its optical resolution was accomplished with the use of (+)- or (-)-2,2'-(1,1'-binaphthyl)phosphoric acid as a resolving agent.

Keywords thromboxane A₂; receptor antagonist; antiallergic; dibenzoxepine; binaphthylphosphoric acid; optical resolution

Thromboxane A₂ (TXA₂) has been considered to be an important mediator in a variety of circulatory disorders including angina, pectoris, thrombosis and asthma. Several drugs with prostanoid or non-prostanoid structure have been reported to possess TXA₂ antagonistic activities.¹⁾ Recently, dibenzoxepine derivatives **1** (KW 3635)²⁾ and **2** (KW4099)³⁾ have been found to be TXA₂ receptor antagonists and they are expected to be very important compounds for the treatment of such diseases. The racemic compound **2** shows antagonistic activity against both TXA₂ and histamine (H₁). So we investigated the optical resolution as well as the practical large-scale synthesis of **2**.

The C–S bond of **2** was readily formed by displacement of the methoxy group by thiol in the presence of an acid catalyst. Thus, reduction of the ketone **3**⁴⁾ with NaBH₄ in tetrahydrofuran (THF)–MeOH at 10 °C for 2 h provided a colorless liquid, which, upon treatment with 6N HCl to pH 1.5 and heating for 2 h at 35 °C, gave 11-methoxydibenzoxepine **4** in 96% yield. Reaction of **4** with a slight

excess of 2-mercaptoethanol and a catalytic amount of MeSO₃H gave the sulfide **5** as colorless crystals in quantitative yield. The hydroxyl group of **5** was converted to methanesulfonate in pyridine and the product was reacted with 4-benzylpiperidine to produce **6**. Compound **6** was converted to the corresponding fumarate **7** (82% yield from **5**). The fumarate **7** was hydrolyzed under alkaline conditions and the resulting sodium salt **2** was isolated as colorless crystals in 90% yield from **7**.

This synthetic method could be employed even on a multikilogram scale without difficulty.

Resolution of the ester **6** has been accomplished efficiently by use of both atropisomers of 2,2'-(1,1'-binaphthyl)phosphoric acid (BNPPA) as resolving agents.⁵⁾ Thus, by using a half equivalent of (+)-BNPPA, the (+)-BNPPA salt of (+)-**6** was separated as colorless crystals first, while subsequently (–)-**6** was obtained as the (–)-BNPPA salt from the mother liquor by using (–)-BNPPA, or *vice versa*. Each salt was recrystallized from CHCl₃–MeOH to nearly 100% optical purity. From the salt, (+)- or (–)-**6** was extracted into the organic phase on partitioning between ethyl acetate and aqueous ammonia, then hydrolyzed to (+)- or (–)-**2** by alkaline treatment without any racemization.

The specific rotations of (+)- and (–)-**2** were +94.1° and –95.8°, respectively ([α]_D²⁰, *c* = 1, MeOH).

Experimental

Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrophotometer. Proton nuclear magnetic resonance (¹H-NMR) spectra were obtained with a Bruker AC-300 spectrometer and signals are given in ppm using tetramethylsilane as an internal standard. Optical rotations

Chart 1

Chart 2

were measured with a Horiba SEPA-200 polarimeter. All melting points were determined on a Mettler FP62 melting point instrument.

Methyl ($\pm$)-11-Methyloxy-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate (4) NaBH_4 (0.70 g, 18.6 mmol) was added in portions to a suspension of **3** (10.0 g, 37.3 mmol) in THF (30 ml) and MeOH (45 ml) with ice-water cooling. After the addition, stirring was continued at the same temperature for 1 h, then the pH of the reaction mixture was adjusted to pH 1 with 6N HCl and the resulting solution was heated at 35°C for 2 h. The solution was cooled and neutralized with 10N NaOH. After evaporation of a half of the solvent, water (30 ml) was added for crystallization. The ester **4** was obtained as colorless crystals (10.2 g, 96%), mp 108–109°C. *Anal.* Calcd for $\text{C}_{17}\text{H}_{16}\text{O}_4$: C, 71.81; H, 5.67. Found: C, 71.80; H, 5.67. IR (KBr): 2950, 1710, 1615 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 3.37 (3H, s, CH_3O), 3.91 (3H, s, $\text{CH}_3\text{O}_2\text{C}$), 4.94 (1H, d, $J=12$ Hz, C(6)-H), 5.06 (1H, s, C(11)-H), 6.18 (1H, d, $J=12$ Hz, C(6)-H), 6.91 (1H, d, $J=8$ Hz, C(4)-H), 7.35–7.38 (4H, m, C(7)-C(10) aromatic H), 7.90 (1H, d, $J=8$ Hz, C(3)-H), 8.07 (1H, s, C(1)-H).

Methyl ($\pm$)-11-(2-Hydroxyethyl)thio-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate (5) 2-Mercaptoethanol (1.30 ml, 18.5 mmol) and methanesulfonic acid (0.11 ml, 1.76 mmol) were added to a solution of **4** (5.00 g, 17.6 mmol) in CH_2Cl_2 (40 ml) at room temperature, then the mixture was heated under reflux for 5 h. After the mixture had cooled, Et_3N (0.25 ml, 1.76 mmol) was added and the solvent was evaporated off. MeOH (30 ml) was added to afford **5** as colorless crystals (5.84 g, 100%), mp 128–129°C. *Anal.* Calcd for $\text{C}_{18}\text{H}_{18}\text{O}_4\text{S}$: C, 65.43; H, 5.49. Found: C, 65.32; H, 5.39. IR (KBr): 3400, 2950, 1750, 1685, 1610 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 2.32 (1H, br, OH), 2.58–2.77 (2H, m, SCH_2), 3.66–3.77 (2H, m, CH_2OH), 3.90 (3H, s, $\text{CH}_3\text{O}_2\text{C}$), 4.94 (1H, d, $J=13$ Hz, C(6)-H), 5.13 (1H, s, C(11)-H), 6.45 (1H, d, $J=13$ Hz, C(6)-H), 6.89 (1H, d, $J=8$ Hz, C(4)-H), 7.22–7.35 (4H, m, C(7)-C(10) aromatic H), 7.83 (1H, d, $J=8$ Hz, C(3)-H), 8.01 (1H, s, C(1)-H).

Methyl ($\pm$)-11-[2-(4-Benzyl-1-piperidinyl)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate, 1 Fumarate (7) Methanesulfonyl chloride (5.74 g, 50.0 mmol) was added to a solution of **5** (11.2 g, 33.9 mmol) in pyridine (41 ml) with ice-water cooling. The mixture was stirred at 5°C for 2 h, then ethyl acetate (56 ml) and water (28 ml) were added and the whole was acidified to pH 3 with concentrated HCl. The organic layer was separated, washed with water and dried over magnesium sulfate. Then 4-benzylpiperidine (11.7 g, 66.7 mmol) was added and the reaction mixture was refluxed for 2 h. After completion of the reaction, brine was added to the mixture. The separated organic layer was concentrated and ethanol (78 ml) was added to the residue. To this ethanolic solution, fumaric acid (4.33 g, 37.3 mmol) was added dissolved at 50°C. On cooling of the solution, the fumarate **7** separated as colorless crystals (17.0 g, 83%), mp 181–182°C. *Anal.* Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_3\text{S} \cdot \text{C}_4\text{H}_4\text{O}_4$: C, 67.64; H, 6.18; N, 2.32. Found: C, 67.54; H, 6.09; N, 2.24. IR (KBr): 2950, 1710, 1690, 1645, 1610 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3 -DMSO- d_6) δ : 1.33–3.06 (15H, m, SCH_2CH_2 , piperidine, CH_2Ar), 3.83 (3H, s, $\text{CH}_3\text{O}_2\text{C}$), 5.00 (1H, d, $J=13$ Hz, C(6)-H), 5.43 (1H, s, C(11)-H), 6.29 (1H, d, $J=13$ Hz, C(6)-H), 6.63 (2H, s, $\text{CH}=\text{CH}$ of fumaric acid), 6.87 (1H, d, $J=8$ Hz, C(4)-H), 7.13–7.39 (9H, m, aromatic H), 7.74 (1H, d, $J=8$ Hz, C(3)-H), 8.23 (1H, s, C(1)-H), 9.96 (2H, br, CO_2H of fumaric acid).

Sodium ($\pm$)-11-[2-(4-Benzyl-1-piperidinyl)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate (2) A solution of **7** (50.0 g, 82.8 mmol) in CH_2Cl_2 (250 ml) and water (150 ml) was stirred and the pH was adjusted to pH 12.5 with 10N NaOH. The organic layer was separated, washed with water and dried over magnesium sulfate. After evaporation of the solvent, isopropanol (450 ml), water (33 ml) and 10N NaOH (8.3 ml) were added to the residue and the mixture was heated under reflux for 2 h. Compound **2** separated as colorless crystals (38.8 g, 95%) from the cooled mixture and was recrystallized from aqueous isopropanol. This product did not show a clear melting point (decomposed over 240°C).

Anal. Calcd for $\text{C}_{29}\text{H}_{30}\text{NNaO}_3\text{S} \cdot \text{H}_2\text{O}$: C, 67.81; H, 6.28; N, 2.73. Found: C, 68.00; H, 6.29; N, 2.65. IR (KBr): 3410, 2950, 1615, 1590, 1550 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) δ : 1.12–2.73 (15H, m, SCH_2CH_2 , piperidine, CH_2Ar), 4.96 (1H, d, $J=13$ Hz, C(6)-H), 5.29 (1H, s, C(11)-H), 6.20 (1H, d, $J=13$ Hz, C(6)-H), 6.69 (1H, d, $J=8$ Hz, C(4)-H), 7.15–7.41 (9H, m, aromatic H), 7.68 (1H, d, $J=8$ Hz, C(3)-H), 7.89 (1H, s, C(1)-H).

Sodium (+)-11-[2-(4-Benzyl-1-piperidinyl)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate [(+)-2] (+)-BNPPA (1.00 g, 2.87 mmol) and CHCl_3 (38 ml) were added to a methanolic solution (0.2 M, 28.7 ml) of the ester ($\pm$)-**6** (5.74 mmol), which was prepared from ($\pm$)-**7** by extraction with CH_2Cl_2 and aqueous NaOH followed by evaporation of CH_2Cl_2 and addition of MeOH. The mixture was heated to form a solution, and crystals were formed on cooling. The optical purity of this material (1.97 g) was 91.2%, as determined by HPLC after extraction with ethyl acetate and aqueous sodium bicarbonate. This (1.95 g) was recrystallized from CHCl_3 (38 ml) and MeOH (20 ml) to obtain colorless crystals (1.67 g, 35% from ($\pm$)-**7**), which showed 100% optical purity by HPLC analysis after extraction as mentioned above. *Anal.* Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_3\text{S} \cdot \text{C}_{20}\text{H}_{13}\text{O}_4\text{P}$: C, 71.84; H, 5.55; N, 1.68. Found: C, 71.61; H, 5.92; N, 1.47.

This optically pure product (1.58 g, 1.89 mmol) was extracted with ethyl acetate (16 ml) and aqueous ammonia (5%, 16 ml), and the organic layer was dried over magnesium sulfate, then the solvent was evaporated off. MeOH (24 ml), water (18 ml) and 10N NaOH (0.38 ml) were added to the residue, and the mixture was refluxed for 1.5 h. After the reaction, a half of MeOH was evaporated off and water (25 ml) was added, then the pH was adjusted to pH 6.0 by adding aqueous HCl. The precipitated free acid was collected by filtration and dissolved in isopropanol (9 ml), water (0.9 ml) and 10N NaOH (0.28 ml) under heating at 60°C, then the solution was allowed to cool. The sodium salt, (+)-**2**, was obtained as colorless crystals (0.61 g, 65% from the diastereomeric salt). $[\alpha]_D^{20} +94.1^\circ$ ($c=1$, MeOH). IR (KBr): 3410, 2950, 1615, 1590, 1550 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) signals were the same as those of ($\pm$)-**2**.

Sodium (–)-11-[2-(4-Benzyl-1-piperidinyl)ethyl]thio-6,11-dihydrodibenz[*b,e*]oxepine-2-carboxylate [(–)-2] This compound was prepared from ($\pm$)-**7** and (–)-BNPPA by the same method employed for the synthesis of (+)-**2**. The (–)-BNPPA salt of (–)-**6** was obtained in 39% yield from ($\pm$)-**7**. *Anal.* Calcd for $\text{C}_{30}\text{H}_{33}\text{NO}_3\text{S} \cdot \text{C}_{20}\text{H}_{13}\text{O}_4\text{P}$: C, 71.84; H, 5.55; N, 1.68. Found: C, 71.62; H, 5.68; N, 1.42. This salt was also obtained by the use of (–)-BNPPA, from the mother liquor of the above-described separation of (+)-**6** (+)-BNPPA.

(–)-**2** was obtained in 77% yield from the diastereomeric salt. $[\alpha]_D^{20} -95.8^\circ$ ($c=1$, MeOH). IR (KBr): 3410, 2950, 1615, 1590, 1550 cm^{-1} . $^1\text{H-NMR}$ (DMSO- d_6) signals were the same as those of ($\pm$)-**2**.

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