Preparation of Optically Active Succinic Acid Derivatives. I. Optical Resolution of 2-Benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)-propionic Acid

Toshiaki YAMAGUCHI,[a] Takashi YANAGI,[a] Hiroshi HOKARI,[a] Yuko MUKAIYAMA,[a] Tetsuhide KAMIJO,*[,a] and Iwao YAMAMOTO[b]

Kissei Pharmaceutical Co., Ltd., Central Research Laboratories,[a] 4365–1 Kashiwabara, Hotaka-machi, Minamiazumi-gun, Nagano 399–83, Japan and Shinshu University,[b] 3–15–1 Tokida, Ueda-shi, Nagano 386, Japan.
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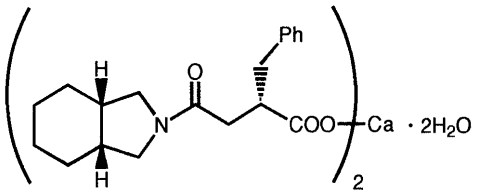
(+)-Monocalcium bis[(2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionate] dihydrate (KAD-1229, 1) is an optically active succinic acid calcium salt derivative with potent hypoglycemic effect. We investigated two optical resolution methods. 2-Benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid 6 was esterified with (*S*)-*N*-benzyl mandelamide and the resulting diastereomeric esters were separated by column chromatography on silica gel to give 7 and 8 in 39.1% and 45.3% yields, respectively. The diastereomer 7 was hydrolyzed to give the optically active acid (−)-6. The absolute configuration of (−)-6 was established as *S* by comparison with an authentic sample. The alternative method was resolution using an optically active amine. Treatment of a solution of the racemic acid 6 with 0.65 eq of (*R*)-1-(1-naphthyl)ethylamine in ethanol gave the salt in 23.2% yield with an optical purity of 96.8% ee.

Key words KAD-1229; potent hypoglycemic effect; optical resolution; (2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-yl-carbonyl)propionic acid

We have developed a novel oral hypoglycemic agent, (+)-monocalcium bis[(2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionate] dihydrate (KAD-1229; **1**), which has a rapid-onset but short-lasting hypoglycemic effect compared with sulfonylureas.[1] Compound **1** inhibits the ATP-sensitive potassium channels in pancreatic B-cells and stimulates insulin release, like sulfonylureas.[1] It is a bicyclic succinic acid derivative with an *S*-configurational asymmetric carbon at the 2-position. Optically active succinic acid derivatives have been synthesized using Evans' chiral enolate methodology.[2] However, this method is disadvantageous for large-scale synthesis, because an expensive chiral source and maintenance of a low temperature are necessary. We require large amounts of optically pure **1** for further evaluation as an antidiabetic drug. Therefore, we investigated optical resolution of (2*RS*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid **6**; the results are described in this paper.

The synthesis of the racemic acid **6** is shown in Chart 1.[3] Thus, benzylidene succinic acid **2** was prepared by condensation of benzaldehyde with diethyl succinate in the presence of sodium ethoxide, followed by hydrolysis, in 70.3% yield. The acid **2** was treated with acetic anhydride to give an anhydride **3** in 60.3% yield. This anhydride **3** was treated with *cis*-hexahydroisoindoline **4**[4] to give the amide **5** in 74.9% yield, and hydrogenation of **5** gave the racemic acid **6** in 90.6% yield.

We investigated two optical resolution methods. One of them involves esterification, *i.e.*, the racemic acid **6** was esterified with optically active D-menthol, (*S*)-phenylethyl alcohol or (*S*)-*N*-benzyl mandelamide, using 1,3-dicyclo-



KAD-1229, 1

Fig. 1

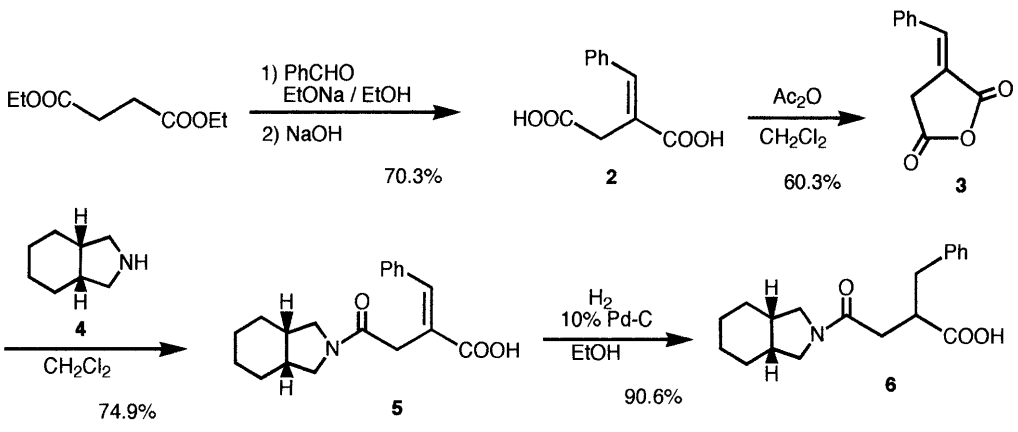


Chart 1

* To whom correspondence should be addressed.

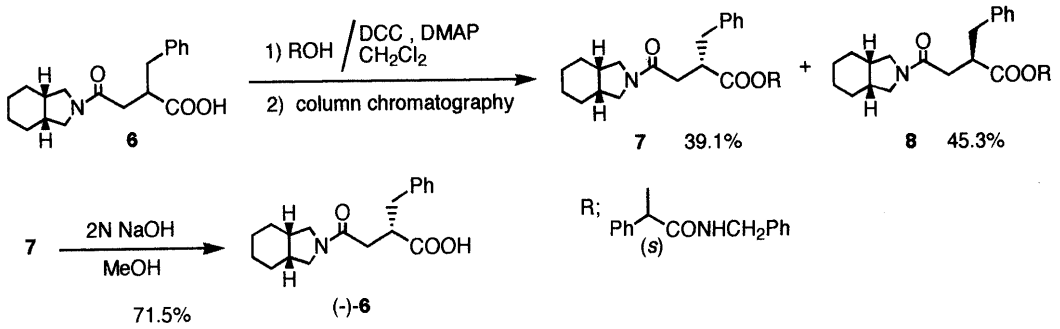


Chart 2

Table 1. Optical Resolution of **6** by Fractional Crystallization Using Chiral Amines

Amine	eq	Solvent	Yield (%)	Optical purity (%ee)
(−)-Cinchonidine	1.0	iso-PrOH	25.5	80.2
(*R*)-1-Phenylethylamine	1.0	AcOEt/EtOH	36.2	70.4
		AcOEt/EtOH	4.2	98.4 (2)
(*R*)-1-(1-Naphthyl)ethylamine	1.0	iso-PrOH	45.5	53.6
		iso-PrOH	30.8	97.0 (1)
(*R*)-1-(1-Naphthyl)ethylamine	0.65	EtOH	23.2	96.8

The number in ( ) was times of recrystallization.

hexyl carbodiimide (DCC), in the presence of *N*,*N*-dimethylaminopyridine (DMAP) as a catalyst. Among the resulting diastereomeric esters, the D-menthyl and (*S*)-phenylethyl esters could not be separated into the diastereomers by column chromatography, but the diastereomeric (*S*)-*N*-benzyl mandelamide ester was separated by column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate = 5/1) to afford the two diastereomers, **7** and **8**, in 39.1% and 45.3% yields, respectively. The diastereomer with the higher *Rf* value, **7**, was hydrolyzed to give optically active acid (−)-**6** ($[\alpha]_D^{24}$ −3.2° (*c* = 1.00, MeOH)) (Chart 2). The optical purity of (−)-**6**, determined by HPLC on Chiralcel OG (Daicel Chemical Ind., Ltd.) of the methyl ester obtained by treatment with trimethylsilyldiazomethane,[5] was 92.0% ee.

The alternative method was optical resolution of racemic **6** using (−)-cinchonidine, (*R*)-1-phenylethylamine or (*R*)-1-(1-naphthyl)ethylamine as an optically active base, with isopropanol, ethyl acetate/ethanol or ethanol as a solvent. A solution of racemic **6** was treated with an equimolar amount of an optically active amine, seeded, and then allowed to stand overnight at room temperature. The precipitated salt was collected by filtration, washed with a small amount of solvent, and then dried. The optical purity of (−)-**6** was determined by the above HPLC method. The results are summarized in Table 1. The resolution was most efficient when (*R*)-1-(1-naphthyl)-ethylamine was used as a base and isopropanol as a solvent; a single recrystallization gave the diastereomer salt in 30.8% yield with an optical purity of 97.0% ee.

Furthermore, treatment of a solution of racemic **6** with 0.65 eq of (*R*)-1-(1-naphthyl)ethylamine in ethanol gave the salt in 23.2% yield with an optical purity of 96.8% ee. The diastereomer salt was treated with 2 N hydrochloric

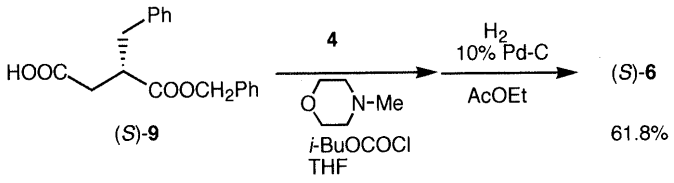


Chart 3

acid to give the optically active acid (−)-**6** in good yield.

The absolute configuration of (−)-**6** was established by comparison with an authentic sample. The authentic sample with *S*-configuration was derived from (*S*)-**9** obtained by Plattner's method.[2] The acid (*S*)-**9** was treated with the amine **4** using isobutyl chloroformate and *N*-methylmorpholine, and the resulting amide was hydrogenated to give the enantiomerically pure acid (*S*)-**6** in 61.8% yield. The value of optical rotation of (*S*)-**6** was $[\alpha]_D^{18}$ −3.5° (*c* = 1.00, MeOH) and the retention time on HPLC was the same as that of (−)-**6**, so that the stereochemistry of (−)-**6** was determined to be *S* (Chart 3).

The (*S*)-(−)-**6** obtained was treated with 2 N sodium hydroxide solution to yield the sodium salt, which was treated with calcium chloride to give KAD-1229, **1**, in 80.2% yield. Both of the above optical resolution methods appear to be useful and practical for the synthesis of large amounts of KAD-1229.

Experimental

All melting points were measured with a Yanagimoto melting point apparatus and are uncorrected. IR spectra were recorded with a Nicolet 510 FT-IR spectrometer. ^{1}H-NMR spectra were recorded with a Bruker AMX-400 (400 MHz). Mass spectra were measured with a JEOL JMS-SX102A mass spectrometer. Optical rotations were measured with a JASCO DIP-370 polarimeter.

(2*RS*)-2-Benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic Acid 6 The amine **4**[4] (10.0 g, 79.9 mmol) was added dropwise to a solution of benzylidene succinic anhydride **3**[3] (13.5 g, 72.5 mmol) in CH_2Cl_2 (75 ml) at 0 °C. After 2 h, the mixture was gradually warmed to ambient temperature, stirred overnight, and then evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give (*E*)-2-benzylidene-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid **5** as colorless crystals, 17.1 g (74.9%), mp 154—156 °C. IR (KBr): 1700, 1600 cm^{-1}. ^{1}H-NMR (DMSO-d_6) δ: 1.3—1.65 (8H, m), 2.1—2.35 (2H, m), 7.4—7.5 (5H, m), 7.75 (1H, s), 12.55 (1H, br s). HR FAB-MS *m*/*z*: Calcd for $C_{19}H_{24}NO_3(M+H)^+$: 314.1767. Found: 316.1756.

A suspension of **5** (17.1 g, 54.6 mmol) and 10% Pd–C (1.7 g) in ethanol (150 ml) was hydrogenated overnight at atmospheric pressure. The Pd–C was filtered off, the filtrate was concentrated *in vacuo*, and the resulting residue was recrystallized from ethyl acetate to give (2*RS*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid **6** as colorless crystals, 15.6 g (90.6%), mp 124—125 °C. IR (KBr): 1730, 1610 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.7 (8H, m), 2.05—2.3 (2H, m), 2.65—3.5

(7H, m), 7.1—7.4 (5H, m). HR FAB-MS *m/z*: Calcd for $C_{19}H_{23}NO_3$ $(M+H)^+$: 316.1913. Found: 316.1901.

(*S*)-(*N*-Benzylcarbamoyl)phenylmethyl (2*S*)-2-Benzyl-3-(*cis*-hexahydroindolin-2-ylcarbonyl)propionate 7 and (*R*)-(*N*-Benzylcarbamoyl)-phenylmethyl (2*S*)-2-Benzyl-3-(*cis*-hexahydroindolin-2-ylcarbonyl)propionate 8 DCC (413 mg, 2.0 mmol) and DMAP (50 mg, 0.4 mmol) were added to a solution of **6** (630 mg, 2.0 mmol) and (*S*)-*N*-benzyl mandelamide (483 mg, 2.0 mmol) in CH_2Cl_2 (20 ml) at 0 °C. After 2 h, the mixture was gradually warmed to room temperature, and then stirred overnight, and filtered. The filtrate was washed with saturated $NaHCO_3$ solution, 1 N HCl and water, and then dried over Na_2SO_4 and finally the solvent was evaporated under reduced pressure. The residue was chromatographed on silica gel (eluent: *n*-hexane/ethyl acetate = 5/1) to give (*S*)-(*N*-benzylcarbamoyl)phenylmethyl (2*S*)-2-benzyl-3-(*cis*-hexahydroindolin-2-ylcarbonyl)propionate **7** as colorless crystals, 421 mg (39.1%), and (*R*)-(*N*-benzylcarbamoyl)phenylmethyl (2*S*)-2-benzyl-3-(*cis*-hexahydroindolin-2-ylcarbonyl)propionate **8** as a white syrup, 488 mg (45.3%).

7: mp 114—115 °C, $[\alpha]_D^{26}$ +19.4° (c = 1.03, MeOH), IR (KBr): 1745, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.2—1.6 (8H, m), 1.9—2.0 (1H, m), 2.1—2.2 (1H, m), 2.4—2.5 (1H, m), 2.65—3.3 (8H, m), 4.4—4.6 (2H, m), 6.05—6.09 (1H, m), 7.05—7.3 (15H, m), 8.4—8.6 (1H, m). HR FAB-MS *m/z*: Calcd for $C_{34}H_{39}N_2O_4(M+H)^+$: 539.2910. Found: 539.2914.

8: $[\alpha]_D^{26}$ +48.6° (c = 1.22, MeOH), IR (KBr): 1750, 1740 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.2—1.6 (8H, m), 2.0—2.1 (1H, m), 2.1—2.2 (1H, m), 2.3—2.45 (1H, m), 2.45—2.6 (1H, m), 2.8—3.35 (7H, m), 4.25—4.35 (1H, m), 4.55—4.65 (1H, m), 6.10 (1H, s), 7.1—7.45 (15H, m), 7.8—8.05 (1H, m). HR FAB-MS *m/z*: Calcd for $C_{34}H_{39}N_2O_4(M+H)^+$: 539.2910. Found: 539.2981.

(2*S*)-2-Benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic Acid 6 A solution of **7** (380 mg, 0.71 mmol) in methanol was treated dropwise with 2 N NaOH (0.88 mmol) at room temperature, followed by stirring overnight. Water was added, and then the aqueous layer was washed with ethyl acetate, neutralized with 2 N HCl (pH 4), and extracted with CH_2Cl_2. The extract was washed with water, dried over Na_2SO_4, and then evaporated under reduced pressure to give (2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid **6** as a viscous oil, 159 mg (71.5%), $[\alpha]_D^{24}$ −3.2° (c = 1.04, MeOH). IR (neat): 1735, 1605 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.7 (8H, m), 2.05—2.3 (2H, m), 2.65—3.5 (7H, m), 7.1—7.4 (5H, m). HR FAB-MS *m/z*: Calcd for $C_{19}H_{23}NO_3(M+H)^+$: 316.1913. Found: 316.1901.

Authentic Sample of (*S*)-6 *N*-Methylmorpholine (0.5 ml, 4.55 mmol) and isobutyl chloroformate (0.38 ml, 2.92 mmol) were added to a solution of (3*S*)-3-benzyloxycarbonyl-4-phenylbutyric acid (*S*)-**9**[2] (671 mg, 2.25 mmol) in THF (15 ml) at −20 °C. The mixture was stirred at −20 °C for 20 min, then the amine **4**[4] (313 mg, 2.50 mmol), was added and the whole was stirred for 1 h. The mixture was concentrated under reduced pressure, ethyl acetate was added to the residue, and then the organic layer was washed with 0.5 N HCl, saturated $NaHCO_3$ solution and brine, and finally dried with $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was recrystallized from CH_2Cl_2/*n*-hexane to give benzyl (2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionate as colorless crystals, 772 mg (84.6%), mp 106—107 °C, $[\alpha]_D^{26}$ −7.6° (c = 1.11, MeOH). IR (KBr): 1735, 1630 cm^{-1}. ^{1}H-NMR ($CDCl_3$): 1.3—1.65 (8H, m), 2.1—2.35 (3H, m), 2.55—2.7 (1 H, m), 2.8—2.9 (1H, m), 3.0—3.45 (6H, m), 5.0—5.2 (2H, m), 7.1—7.4 (10H, m). HR FAB-MS *m/z*: Calcd for $C_{26}H_{32}NO_3(M+H)^+$: 406.2382. Found: 406.2382.

A suspension of benzyl (2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionate (400 mg, 0.99 mmol) and 10% Pd–C (60 mg) in ethyl acetate (3 ml) was hydrogenated at atmospheric pressure for 16 h. The Pd–C was filtered off, and the filtrate was concentrated *in vacuo* to give (2*S*)-2-benzyl-3-(*cis*-hexahydroisoindolin-2-ylcarbonyl)propionic acid **6**, 227 mg (73.0%), $[\alpha]_D^{18}$ −3.5° (c = 1.00, MeOH).

Resolution of 6 with (*R*)-1-(1-Naphthyl)ethylamine Racemic **6** (3.0 g, 9.51 mmol) and (*R*)-1-(1-naphthyl)ethylamine (1.62 g, 9.51 mmol) were dissolved in isopropanol (60 ml) with heating, seeded, and then allowed to stand overnight. The precipitated salt was filtered, washed with isopropanol, and then dried under reduced pressure to give the salt (2.10 g, 45.5%) of 53.6% ee. Similarly, this salt was dissolved in isopropanol (33 ml) with heating, seeded, and then allowed to stand overnight. The precipitated salt was filtered, washed with isopropanol, and then dried under reduced pressure to give the salt (1.42 g, 30.8%) of 97.0% ee.

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