

## Preparation of Optically Active Succinic Acid Derivatives. II.<sup>1)</sup> Efficient and Practical Synthesis of KAD-1229

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For large-scale synthesis of monocalcium bis[(2*S*)-2-benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionate]dihydrate (**1**, KAD-1229), we investigated regioselective reactions of (*S*)-2-benzylsuccinic acid (**2**) with *cis*-hexahydroisindoline (**4**). It was difficult to obtain a half amide regioselectively through coupling reaction of the (*S*)-acid **2** with the amine **4**. Therefore, the succinic acid **2** was converted to bis-activated esters **3a–c** and these were reacted with **4** to give the amides **5a–c** in good yields, regioselectively. The amides **5a–c** were derived to KAD-1229, which has a potent hypoglycemic effect, in good yields.

**Key words** KAD-1229; potent hypoglycemic effect; (*S*)-2-benzylsuccinic acid; (2*S*)-2-benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionic acid

Recently, we found that a newly synthesized monocalcium bis[(2*S*)-2-benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionate] dihydrate (**1**, KAD-1229) has a potent hypoglycemic effect, even though this agent has no sulfonylurea moiety.<sup>2)</sup> Its effect is rapid and short-lasting, so we considered a large amount of **1**, KAD-1229, would be required for further evaluation as an antidiabetic agent.

Previously, we reported the preparation of optically active **8**.<sup>1)</sup> In that paper, we described the resolution of the racemic acid **8** into optical isomers by mean of two diastereomer separation methods, using the salt with optically active amine and using the ester with optically active alcohol. However, the chemical yields of these resolution methods were low. We investigated an alternative method, *i.e.*, the regioselective reaction of optically active 2-benzylsuccinic acid with *cis*-hexahydroisindoline (**4**).<sup>3)</sup> In this paper, we report a synthetic method for bis-activated esters of optically active 2-benzylsuccinic acid and their regioselective amidation to obtain KAD-1229.

It is known that asymmetric hydrogenation of *E*-benzylidene succinic acid using a chiral diphosphine complex of rhodium or ruthenium gives an optically active 2-benzylsuccinic acid, enantioselectively.<sup>4)</sup> Since a mixture of *E* and *Z* isomers of benzylidene succinic acid which was obtained easily from succinic acid, was hydrogenated with 10% palladium charcoal to give a racemic acid in good yield, we examined optical resolution of racemic 2-benzylsuccinic acid using optically active amine. The racemic acid and (*S*)-1-phenyl-2-(4-tolyl)ethylamine, (*R*)-1-(1-naphthyl)ethylamine, or (*R*)-1-phenylethylamine were dissolved in ethanol, seeded and allowed to stand overnight at room temperature. The salt formed was collected by filtration and recrystallized from ethanol to give the amine salt of the optically active acid **2**, in 24.4% yield (96.8% ee), 20.7% yield (99.2% ee), and 19.8% yield (99.5% ee), respectively. The obtained salt was treated with 2*N* hydrochloric acid to give the optically active acid **2** in 90% yield. The optical purity of **2** was determined by HPLC using a chiral column, after the transformation of **2** to the corresponding dimethyl ester by treatment with trimethylsilyldiazomethane.<sup>5)</sup> The results of optical

resolution are summarized in Table 1.

In order to obtain KAD-1229 effectively, we investigated regioselective transformations of readily available optically active (*S*)-2-benzylsuccinic acid (**2**) to its half amide. Generally, it is difficult to obtain a half amide regioselectively through coupling reaction of 2-alkylsuccinic acid with amine, because 2-alkylsuccinic acid yields an anhydride easily *in situ*, and the anhydride would react with amine non-regioselectively. Indeed, reaction of the acid **2** and the amine **4** in the presence of dicyclohexylcarbodiimide (DCC) in methylene chloride gave a mixture of regioisomers in the ratio of 1 to 1. On the other hand, it is well known that the reactions of activated ester derivatives of carboxylic acid with amines give amides. For instance, esters of carboxylic acid with *p*-nitrophenol, *N*-hydroxysuccinimide (HOSu), and *endo-N*-hydroxy-5-norbornene-2,3-dicarboximide (HONB) are used for peptide synthesis. We also reported the regioselective reaction of the primary carboxylic acid moiety of (*R*)-2-(1-naphthyl)methylsuccinic acid with morpholine.<sup>6)</sup> Therefore, we expected that the bis-activated esters **3** of succinic acid **2**, which do not form the anhydride *in situ*, might

Table 1. Optical Resolution of 2-Benzylsuccinic Acid Using Chiral Amines

| Amine                                        | Equiv. | Solvent | Yield (%) | Optical purity (% ee) |
|----------------------------------------------|--------|---------|-----------|-----------------------|
| ( <i>R</i> )-1-Phenylethylamine              | 2.0    | EtOH    | 50.9      | 42.1                  |
|                                              |        | EtOH    | 19.8      | 99.5 (2)              |
| ( <i>R</i> )-1-(1-Naphthyl)ethylamine        | 1.0    | EtOH    | 30.8      | 86.5                  |
|                                              |        | EtOH    | 20.7      | 99.2 (1)              |
| ( <i>S</i> )-1-Phenyl-2-(4-tolyl)-ethylamine | 1.0    | EtOH    | 40.9      | 49.6                  |
|                                              |        | EtOH    | 24.4      | 96.8 (1)              |
| Quinine                                      | 1.0    | EtOH    | 46.6      | 59.8                  |
|                                              |        | EtOH    | 12.4      | 99.2 (4)              |
| ( <i>R</i> )-Phenylglycinol                  | 1.0    | EtOH    | 45.6      | 36.3                  |
|                                              |        | EtOH    | 5.1       | 99.2 (4)              |
| ( <i>R</i> )-Phenylalaninol                  | 1.0    | EtOH    | 30.1      | 53.6                  |
|                                              |        | EtOH    | 3.6       | 99.5 (4)              |

The number in parentheses is the number of recrystallizations.

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react regioselectively with the amine at the less hindered primary carbonyl group.

Reaction of HONB with thionyl chloride in the presence of triethylamine in methylene chloride at 0 °C, followed by addition of **2**, gave a bis-activated ester **3c** in 88% yield. When HOSu, *p*-nitrophenol, and *N*-hydroxybenzotriazole (HOBt) were used instead of HONB, the corresponding bis-esters were obtained in good yields (Table 2). The esters **3a–d** were reacted with the amine **4** in dichloromethane at 0 °C to afford the amides **5a–d** in good yields. The

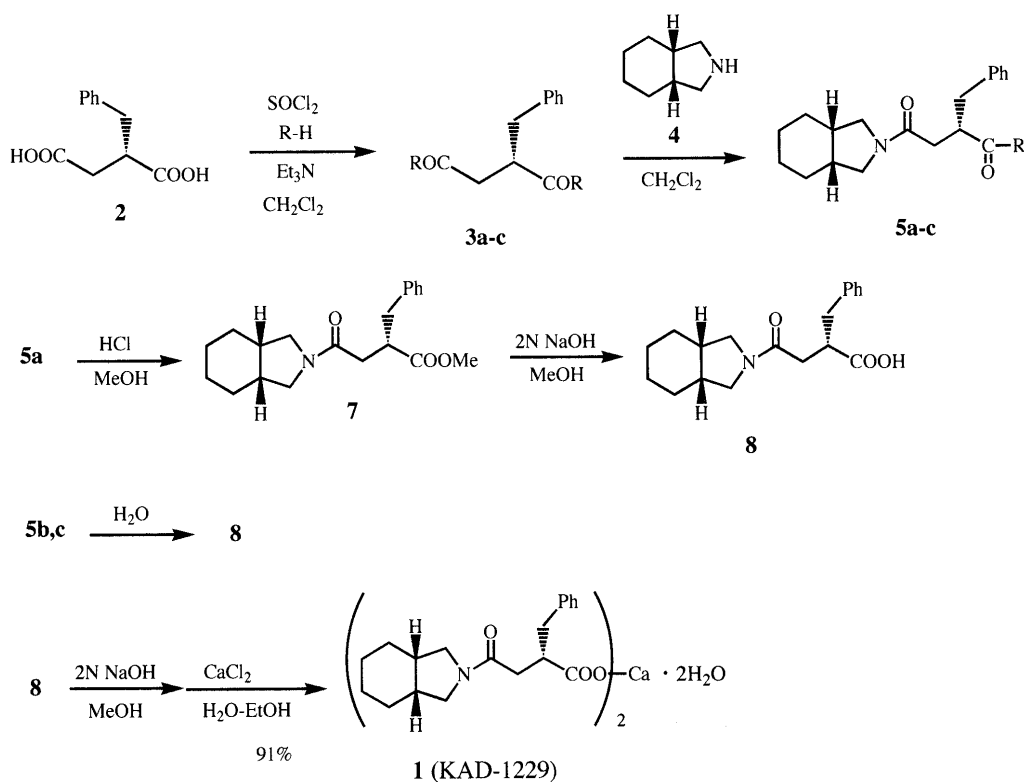
ratio of **5** and **6** was determined by HPLC. The results are summarized in Table 3. Reactions of the HOSu ester **3b** and HONB ester **3c** with **4** gave the amides **5b**, **6b** and **5c**, **6c** in 90% and 94% yields in the ratios of 99.0 to 1.0 and 99.4 to 0.6, respectively. Reaction of the *p*-nitrophenyl ester **3a** with **4** gave the amide **5a** exclusively in 80% yield. But, with HOBt ester, the regioselectivity of the reaction was less than those of the others (**5d** : **6d** = 75.3 : 24.7). The

Table 3. Regioselectivity of the Reaction of Bis-activated Esters **3a–d** with the Amine **4** in CH<sub>2</sub>Cl<sub>2</sub>

Table 2. Physical Data for Bis-activated Esters **3a–d**

| $  \begin{array}{c}  \text{SOCl}_2 \\  \text{R-H} \\  \text{Et}_3\text{N} \\  \text{CH}_2\text{Cl}_2  \end{array}  \xrightarrow{\quad}  \begin{array}{c}  \text{Ph} \\    \\  \text{ROC}-\text{CH}_2-\text{CH}-\text{COR} \\    \\  \text{3}  \end{array}  $ |   |           |        |                                              |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---|-----------|--------|----------------------------------------------|
| <b>3</b>                                                                                                                                                                                                                                                     | R | Yield (%) | mp     | $[\alpha]_D^{25}$                            |
| <b>3a</b>                                                                                                                                                                                                                                                    |   | 97        | 129 °C | −16.0° ( <i>c</i> = 1.0, CHCl <sub>3</sub> ) |
| <b>3b</b>                                                                                                                                                                                                                                                    |   | 97        | 159 °C | −1.6° ( <i>c</i> = 1.0, CHCl <sub>3</sub> )  |
| <b>3c</b>                                                                                                                                                                                                                                                    |   | 88        | 220 °C | +1.5° ( <i>c</i> = 1.0, CHCl <sub>3</sub> )  |
| <b>3d</b>                                                                                                                                                                                                                                                    |   | 79        | 138 °C | +6.3° ( <i>c</i> = 1.0, CHCl <sub>3</sub> )  |

| $  \begin{array}{c}  \text{3a-d} \xrightarrow[\text{CH}_2\text{Cl}_2]{\text{4}} \text{5a-d} + \text{6a-d}  \end{array}  $ |           |           |  |
|---------------------------------------------------------------------------------------------------------------------------|-----------|-----------|--|
| R                                                                                                                         | Yield (%) | 5/6       |  |
| <b>a</b>                                                                                                                  | 80        | 100/0     |  |
| <b>b</b>                                                                                                                  | 90        | 99.0/1.0  |  |
| <b>c</b>                                                                                                                  | 94        | 99.4/0.6  |  |
| <b>d</b>                                                                                                                  | 91        | 75.3/24.7 |  |



Chart

resultant amides **5a—c** were derived to KAD-1229 (Chart). The amides **5b** and **5c** were hydrolyzed with 2N NaOH to give the carboxylic acid **8**. Hydrolyzed HOSu and HONB could be easily removed by extraction. The optical purity of the acid **8** was measured by HPLC<sup>1)</sup> after methyl esterification with trimethylsilyldiazomethane. The acid **8** obtained from **5b** showed 99.6% ee, and that from **5c** showed 99.7% ee. On the other hand, hydrolysis of the amide **5a** with 2N NaOH gave a mixture of the carboxylic acid **8** and *p*-nitrophenol, but the components could not be separated by extraction. Therefore, the amide **5a** was treated with hydrogen chloride in methanol to transform it to the methyl ester **7**, which could be separated from *p*-nitrophenol by extraction. The optical purity of **7** was 97.5% ee. The methyl ester **7** was hydrolyzed with 2N NaOH to give the carboxylic acid **8** in 95% yield. This acid **8** was treated with 2N NaOH, followed by treatment with calcium chloride to give **1** (KAD-1229) in 91% yield.

In summary, this study has shown that bis-activated esters **3a—c**, readily obtainable from optically active (*S*)-2-benzylsuccinic acid (**2**), react with the amine **4** to give amides **3a—c** in good yields, regioselectively and without racemization. The amides **3a—c** were converted to KAD-1229. This method should be useful and practical for the synthesis of large amounts of **1** (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. <sup>1</sup>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.

**Resolution of 2-Benzylsuccinic Acid** Racemic 2-benzylsuccinic acid (2.08 g, 10 mmol) and optically active amine (10 mmol) were dissolved in ethanol with heating, then the solution was seeded, and allowed to stand overnight. The formed salt was collected by filtration, washed with ethanol, and then dried under reduced pressure to give the salt. Similarly, this salt was dissolved in ethanol with heating, and the solution was seeded, then allowed to stand overnight. The formed salt was collected by filtration, washed with ethanol, and dried under reduced pressure to give the salt.

The salt was treated with 2N hydrochloric acid for 1 h to give the acid **2** (quant.), and treatment of the acid **2** with trimethylsilyldiazomethane in MeOH/CH<sub>2</sub>Cl<sub>2</sub> = 1/1 for 0.5 h gave the dimethyl ester of the acid **2**. The optical purity of the dimethyl ester was determined by HPLC (column, Chiralcel OD (Daicel Chemical Ind., Ltd.); elution, hexane/isopropanol (98/2), 1.0 ml/min; 25 °C; retention times, (*R*)-isomer *ca.* 14 min, (*S*)-isomer *ca.* 17 min). The results are summarized in Table 1.

**Preparation of Bis-activated Esters 3a—d** Thionyl chloride (0.15 ml, 4 mmol) was added dropwise to a solution of the appropriate hydroxyl compound (4 mmol) and triethylamine (0.56 ml, 4 mmol) in dichloromethane (10 ml) while the temperature was kept below 5 °C, followed by stirring at 0 °C for 1 h. Succinic acid (**2**) (208 mg, 1 mmol) was added to the reaction mixture, then the whole was gradually warmed to room temperature, stirred overnight and concentrated *in vacuo*. Ethyl acetate was added to the resulting residue. The ethyl acetate layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate/hexane to give the corresponding bis-activated esters **3a—d**. The yield, melting point, and specific rotation data are summarized in Table 2.

**3a:** IR (KBr): 1770, 1745, 1527, 1522 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.88 (1H, dd, *J* = 4.4, 17.4 Hz), 3.0—3.15 (2H, m), 3.24 (1H, dd, *J* = 6.9, 13.7 Hz), 3.55—3.65 (1H, m), 7.10 (2H, d, *J* = 9.2 Hz), 7.2—7.45 (7H, m), 8.23 (2H, d, *J* = 9.2 Hz), 8.27 (2H, d, *J* = 9.2 Hz). *Anal.* Calcd for C<sub>23</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>: C, 61.33; H, 4.03; N, 6.22. Found: C, 61.10; H, 3.98; N, 6.24.

**3b:** IR (KBr): 1812, 1791, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 2.8—2.9

(9H, m), 3.04 (1H, dd, *J* = 7.6, 17.4 Hz), 3.07 (1H, dd, *J* = 7.4, 17.1 Hz), 3.30 (1H, dd, *J* = 6.3, 17.1 Hz), 3.53 (1H, m), 7.2—7.4 (5H, m). *Anal.* Calcd for C<sub>19</sub>H<sub>18</sub>N<sub>2</sub>O<sub>8</sub>: C, 56.72; H, 4.51; N, 6.96. Found: C, 56.40; H, 4.34; N, 6.90.

**3c:** IR (KBr): 1828, 1817, 1780, 1733 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.55 (2H, d, *J* = 9.0 Hz), 1.80 (2H, dd, *J* = 1.3, 8.9 Hz), 2.74 (1H, dd, *J* = 6.9, 17.4 Hz), 2.96 (1H, dd, *J* = 7.0, 17.4 Hz), 3.07 (1H, dd, *J* = 7.0, 14.0 Hz), 3.24 (1H, dd, *J* = 6.4, 14.1 Hz), 3.34 (4H, s), 3.4—3.5 (5H, m), 6.22 (2H, s), 6.23 (2H, s), 7.2—7.4 (5H, m). *Anal.* Calcd for C<sub>29</sub>H<sub>26</sub>N<sub>2</sub>O<sub>8</sub>: C, 65.65; H, 4.94; N, 5.28. Found: C, 65.42; H, 5.03; N, 5.21.

**3d:** IR (KBr): 1805, 1728 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.1—3.2 (1H, m), 3.4—3.6 (2H, m), 3.65—3.9 (2H, m), 7.25—7.45 (7H, m), 7.5—7.65 (2H, m), 7.75—7.85 (1H, m), 7.95—8.1 (2H, m), 8.35—8.45 (1H, m). *Anal.* Calcd for C<sub>23</sub>H<sub>18</sub>N<sub>6</sub>O<sub>4</sub>: C, 62.44; H, 4.10; N, 18.99. Found: C, 62.62; H, 4.11; N, 19.18.

**The Reaction of Bis-activated Esters 3a—d with the Amine 4** A solution of **4** in dichloromethane was added dropwise to a solution of bis-activated esters **3a—d** in dichloromethane at 0 °C. The mixture was warmed gradually to room temperature, stirred overnight, and concentrated under reduced pressure. Ethyl acetate was added to the residue, and the ethyl acetate layer was washed successively with water, 0.5N NaOH, and water, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to give a mixture of the corresponding amides **5a—d** and **6a—d**.

The mixture was subjected to hydrolysis to give a mixture of acids then the ratio of the acids was determined by HPLC (column, SUMICHIRAL OA-3100 (Sumika Chemical Analysis Service, Ltd.); elution, hexane/chloroform/methanol/trifluoroacetic acid (80/18/2/0.2) at 1.0 ml/min; 25 °C). The results are summarized in Table 3.

**5a:** White crystals, mp 114 °C (ethyl acetate/hexane), [ $\alpha$ ]<sub>D</sub><sup>25</sup> -44.0° (*c* = 1.0, CHCl<sub>3</sub>). IR (KBr): 1761, 1633, 1525 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.3—1.65 (8H, m), 2.1—2.4 (2H, m), 2.45—2.6 (1H, m), 2.7—2.8 (1H, m), 2.9—3.0 (1H, m), 3.05—3.15 (1H, m), 3.15—3.25 (1H, m), 3.3—3.5 (4H, m), 7.05—7.15 (2H, m), 7.2—7.4 (5H, m), 8.15—8.25 (2H, m). *Anal.* Calcd for C<sub>25</sub>H<sub>28</sub>N<sub>2</sub>O<sub>5</sub>: C, 68.79; H, 6.47; N, 6.42. Found: C, 68.76; H, 6.43; N, 6.34.

**5b:** Colorless oil, [ $\alpha$ ]<sub>D</sub><sup>25</sup> +4.2° (*c* = 0.65, CHCl<sub>3</sub>). IR (neat): 1812, 1783, 1740 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.3—1.6 (8H, m), 2.1—2.3 (2H, m), 2.42 (1H, dd, *J* = 6.4, 16.3 Hz), 2.6—3.9 (12H, m), 7.1—7.4 (5H, m). HR FAB-MS *m/z*: Calcd for C<sub>23</sub>H<sub>29</sub>N<sub>2</sub>O<sub>5</sub> (M + H)<sup>+</sup>: 413.2076. Found: 413.2076.

**5c:** Colorless oil, [ $\alpha$ ]<sub>D</sub><sup>25</sup> +1.1° (*c* = 1.0, CHCl<sub>3</sub>). IR (neat): 1808, 1777, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.3—1.6 (9H, m), 1.77 (1H, d, *J* = 9.0 Hz), 2.1—2.2 (2H, m), 2.3—2.4 (1H, m), 2.5—2.7 (1H, m), 2.9—3.0 (1H, m), 3.09 (1H, dd, *J* = 6.3, 9.8 Hz), 3.1—3.5 (8H, m), 3.60 (1H, s), 6.19 (2H, s), 7.2—7.3 (5H, m). HR FAB-MS *m/z*: Calcd for C<sub>28</sub>H<sub>33</sub>N<sub>2</sub>O<sub>5</sub> (M + H)<sup>+</sup>: 477.2389. Found: 477.2369.

**(2S)-2-Benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionic Acid (8) from 5b** A solution of the amide **5b** (685 mg, 1.66 mmol) in methanol (22 ml) was treated with 2N NaOH (2.0 ml, 4.0 mmol) at room temperature, and the mixture was stirred for 15 h, then evaporated *in vacuo*. The residue was dissolved in water, and the aqueous layer was washed with ethyl acetate, neutralized with 6N HCl, and extracted with ethyl acetate. The organic layer was washed with water and then dried over Na<sub>2</sub>SO<sub>4</sub>. The solvent was evaporated under reduced pressure to give **8**, 471 mg (90%) as a viscous oil, [ $\alpha$ ]<sub>D</sub><sup>24</sup> -3.5° (*c* = 1.04, methanol). IR (neat): 1735, 1605 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) 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<sub>19</sub>H<sub>26</sub>NO<sub>3</sub> (M + H)<sup>+</sup>: 316.1913. Found: 316.1901.

**(2S)-2-Benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionic Acid (8) from 5c** Using **5c** instead of **5b**, the acid **8** was obtained in 90% yield, as described above for **8** from **5b**.

**Methyl (2S)-2-Benzyl-3-(*cis*-hexahydroisindolin-2-ylcarbonyl)propionate (7)** A suspension of the amide **5a** (8.84 g, 19.4 mmol) in methanol (60 ml) was treated with 6N HCl methanol solution (6.5 ml, 39 mmol), and the mixture was stirred overnight, then evaporated *in vacuo*. The residue was dissolved in ethyl acetate, and the resulting solution was washed successively with 0.5N NaOH (7 times), 1N HCl and water, then dried over Na<sub>2</sub>SO<sub>4</sub>, and the solvent was evaporated under reduced pressure to give the methyl ester **7** as a colorless oil, 6.4 g (quant.). [ $\alpha$ ]<sub>D</sub><sup>25</sup> +1.1° (*c* = 1.0, CHCl<sub>3</sub>). IR (neat): 1808, 1777, 1738 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.2—1.6 (8H, m), 2.1—2.35 (3H, m), 2.55—2.65 (1H, m), 2.75—2.85 (1H, m), 3.0—3.1 (1H, m), 3.1—3.45 (5H, m), 3.6—3.7 (3H, m), 7.15—7.3 (5H, m). HR FAB-MS *m/z*: Calcd for C<sub>20</sub>H<sub>28</sub>NO<sub>3</sub> (M + H)<sup>+</sup>: 330.2069. Found: 330.2079.

**(2S)-2-Benzyl-3-(cis-hexahydroisoindolin-2-ylcarbonyl)propionic Acid (8) from 7** Using **7** instead of **5b**, the acid **8** was obtained quantitatively.

**Monocalcium Bis[(2S)-2-benzyl-3-(cis-hexahydroisoindolin-2-ylcarbonyl)propionate] Dihydrate (1, KAD-1229)** A solution of the acid **8** (4.04 g, 12.8 mmol) in ethanol (15 ml) was treated with 2 N NaOH solution (6.4 ml, 12.8 mmol), and the reaction mixture was evaporated *in vacuo*. The residue was dissolved in water (30 ml) and then a solution of CaCl<sub>2</sub> (2.84 g, 51.2 mmol) in water (10 ml) was added to it, followed by vigorous stirring for an hour. Then the reaction mixture was extracted with five 20 ml portions of CHCl<sub>3</sub>, and the organic layer was washed with water, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure. The residue was recrystallized from 5% aqueous ethanol to give **1** (KAD-1229) as colorless crystals, 4.1 g (91%), mp 179–185 °C,  $[\alpha]_D^{18} + 5.7^\circ$  (*c* = 1.0, methanol). IR (KBr): 1660, 1625 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 1.15–1.5 (16H, m), 1.9–2.4 (6H, m), 2.55–3.1 (14H, m), 3.2–3.5 (6H, m), 7.1–7.3 (10H, m).

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