A practical synthesis of enantiopure N-carbobenzyloxy-N′-phthaloyl-cis-1,2-cyclohexanediamine by asymmetric reductive amination and the Curtius rearrangement

Graphical Abstract

A practical synthesis of enantiopure *N*-carbobenzyloxy-*N'*-phthaloyl-*cis*-1,2-cyclohexanediamine by asymmetric reductive amination and the Curtius rearrangement

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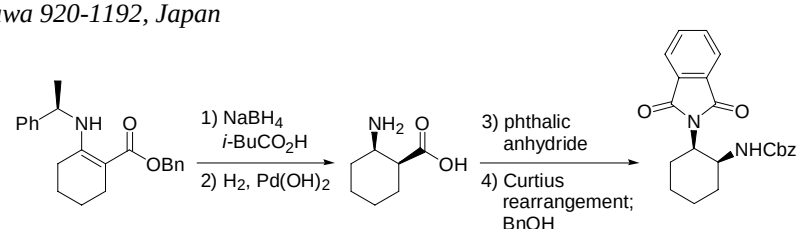
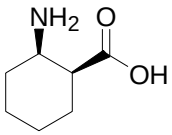


Stereochemistry Abstract

J. Matsuo,* M. Okano, K. Takeuchi, H. Tanaka and H. Ishibashi*

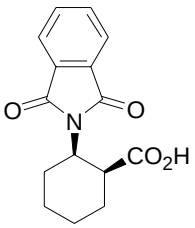


$C_7H_{13}NO_2$

(1*S*,2*R*)-2-Aminocyclohexanecarboxylic acid

Ee = >99%
$[\alpha]_D^{29}$ = +20.2 (*c* 0.25, H_2O)
Source of chirality: asymmetric synthesis
Absolute configuration: (1*S*,2*R*)

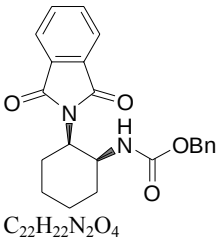
J. Matsuo,* M. Okano, K. Takeuchi, H. Tanaka and H. Ishibashi*



$C_{15}H_{15}NO_4$
(1*S*,2*R*)-2-Phthalimidocyclohexanecarboxylic acid

Ee = >99%
$[\alpha]_D^{28}$ = +98.3 (*c* 1.00, MeOH)
Source of chirality: asymmetric synthesis
Absolute configuration: (1*S*,2*R*)

J. Matsuo,* M. Okano, K. Takeuchi, H. Tanaka and H. Ishibashi*

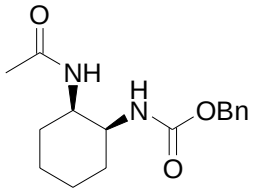


$C_{22}H_{22}N_2O_4$

(1*S*,2*R*)-1-(*N*-Benzyloxycarbonylamino)-2-phthalimidocyclohexane

Ee = >99%
$[\alpha]_D^{29}$ = +92.1 (*c* 0.10, MeOH)
Source of chirality: asymmetric synthesis
Absolute configuration: (1*S*,2*R*)

J. Matsuo,* M. Okano, K. Takeuchi, H. Tanaka and H. Ishibashi*



Ee = >99%
$[\alpha]_D^{29}$ = +33.6 (*c* 0.10, MeOH)
Source of chirality: asymmetric synthesis
Absolute configuration: (1*S*,2*R*)

$C_{16}H_{22}N_2O_3$

(1*S*,2*R*)-1-(*N*-Benzyloxycarbonylamino)-2-acetamidecyclohexane

TETRAHEDRON:
ASYMMETRY

A practical synthesis of enantiopure *N*-carbobenzyloxy-*N'*-phthaloyl-*cis*-1,2-cyclohexanediamine by asymmetric reductive amination and the Curtius rearrangement

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Abstract—Enantiomerically pure *N*-carbobenzyloxy-*N*'-phthaloyl-*cis*-1,2-cyclohexanediamine was synthesized by asymmetric reduction of β-enamino ester formed from benzyl 2-oxocyclohexanecarboxylate and (*R*)-phenylethylamine, followed by hydrogenolysis, phthaloylation and the Curtius rearrangement.

1. Introduction

Asymmetrically *N*-substituted *cis*-1,2-cylohexanediamines are important chiral building blocks for conformationally preorganized peptide nucleic acids[1] and for biologically active small molecules such as NOC-797 (**1**) as an antipruritic agent,[2] MEN-11467 (**2**) as a tachykinin NK_1 antagonist,[3] and MEN-13918 (**3**) as a tachykinin NK_2 antagonist[4] (Figure 1).

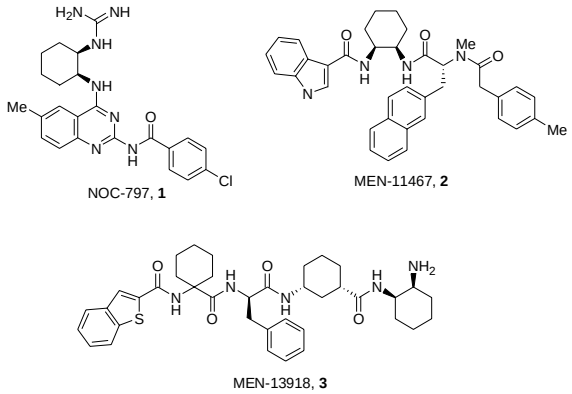
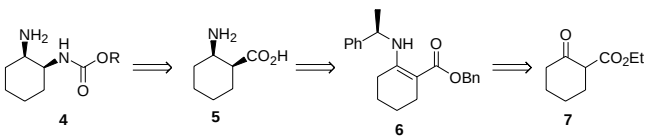


Figure 1. Bioactive small molecules bearing a chiral unit composed of *cis*-1,2-cyclohexanediamine.

These chiral *cis*-1,2-cyclohexanediamines have been synthesized[1] from chiral *trans*-2-azidocyclohexanol,[5] which was prepared by lipase-mediated enzymatic hydrolysis of the corresponding racemic esters.[6] Recently, enantioselective desymmetrization of *meso*-1,2-cyclohexanediamine derivatives has been reported.[7] Due to their unique conformational properties, the use of chiral *cis*-1,2-cyclohexanediamines is expected to increase in various research fields, especially in medicinal chemistry. Therefore, a more efficient method for their preparation should be developed. We planned the synthesis of enantiomerically pure *N*-protected *cis*-1,2-cylohexanediamines **4** from *cis*-2-amino-1-cyclohexanecarboxylic acid (**5**) by the Curtius rearrangement because **5** was readily prepared in a large scale by Palmieri's asymmetric reduction[8] of β-enamino ester **6** (Scheme 1).[9]



Scheme 1. Synthetic plan for **4**.

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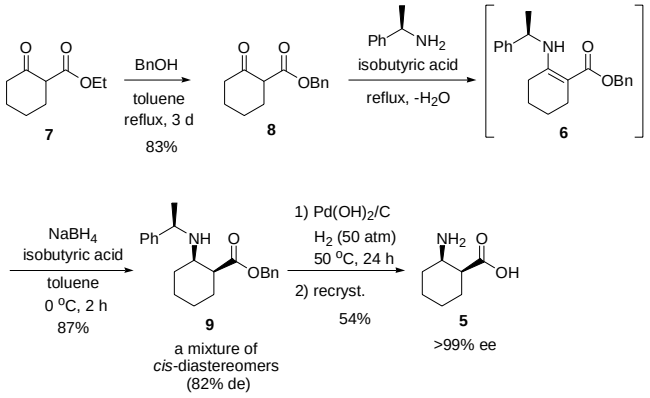
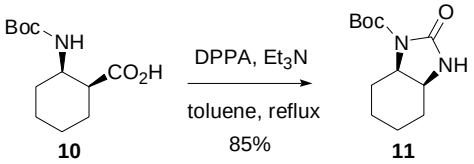
2. Results and discussion

We started the synthesis of **4** by transesterification of commercially available ethyl 2-oxocyclohexanecarboxylate (**7**) with benzyl alcohol in refluxing toluene without any catalyst[10] to afford **8** in 83% yield (Scheme 2). Asymmetric reductive amination of **8** was performed by Xu's protocol.[11] That is, compound **6** was prepared in situ from (*R*)-phenylethylamine and **8** in the presence of isobutyric acid, and the resulting β-enamino ester **6** was reduced with sodium borohydride-isobutyric acid at 0 °C in toluene to afford, in 87% yield, a mixture[12] of two *cis*-diastereomers including amine **9** as a major stereoisomer. Its diastereomeric excess (82% de) was determined by ^{1}H NMR analysis referring to NMR spectra of all four diastereoisomers of the corresponding ethyl ester.[11] Hydrogenolysis of two benzylic groups of thus-obtained *cis*-diastereomers with Perlman's catalyst followed by recrystallization with acetone-water gave enantiomerically pure **5** in 73% yield. Enantiomeric purity of **5** was checked by comparison with reported optical rotation[13] and chiral HPLC analysis of *N*-Cbz derivative of **5**.



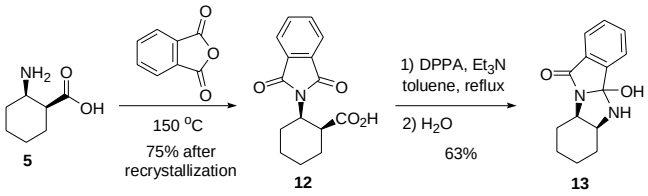
Scheme 2. Synthesis of **5** by asymmetric reductive amination.

Next, suitable protection of the amino group of **5** and the following Curtius rearrangement[14] were investigated. β-Amino acid **5** was protected with the Boc group, and the Curtius rearrangement of *N*-Boc derivative **10** with diphenylphosphoryl azide (DPPA)[15] in refluxing toluene gave cyclic urea **11** in 85% yield (Scheme 3).[16] The phthalimide group was then chosen as a protecting group for the β-amino acid **5**.



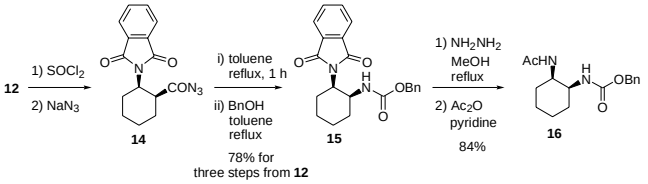
Scheme 3. The Curtius rearrangement of *N*-Boc derivative **10**.

Reaction of **5** with phthalic anhydride[17] and recrystallization from hexane-ethyl acetate gave **12** in 75% yield, and optical purity of **12** was confirmed by chiral HPLC analysis (>99% ee). The Curtius rearrangement of **12** with DPPA followed by hydrolysis of the corresponding isocyanate gave **13** as a mixture of two diastereomers in 63% yield (Scheme 4). Further derivatization (e.g., *N*-acetylation) of **13**, however, did not proceed.



Scheme 4. The Curtius rearrangement of **12** followed by hydrolysis of formed isocyanate to **13**.

We next tried to trap the the intermediate isocyanate group with alcohol to form a carbamate (Scheme 5). Carboxylic acid **12** was converted to the corresponding acyl chloride, and it was reacted with sodium azide to form acyl azide **14**. It was found that the Curtius rearrangement of **14**[18] proceeded in reluxing toluene to afford the corresponding isocyanate, and isocyanate was allowed to react with benzyl alcohol[19] to afford *N*-Cbz derivative **15**[20] in 78% yield for three steps from **12**. Orthogonal reactivity between *N*-Cbz and *N*-phthaloyl group was demonstrated by deprotection of the phthaloyl group with hydrazine in refluxing methanol followed by acetylation to give *N*-acetylated product **16**[20] in 84% yield.



Scheme 5. The Curtius rearrangement of **14** followed by the reaction with benzyl alcohol.

3. Conclusion

In conclusion, enantiomerically pure *N*-carbobenzyloxy-*N*'-phthaloyl-*cis*-1,2-cyclohexanediamine (**15**) was synthesized by diasetereoselective reduction of a β-enamino ester employing inexpensive chiral phenylethylamine as a chiral auxiliary. The appropriately *N*-protected compound **15** would be useful for preparing a chiral unit composed of *cis*-cyclohexanediamine.

4. Experimental

4.1. General methods

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR)

spectra were recorded on a Shimadzu FTIR-8100. ^{1}H NMR spectra were recorded on a JEOL JNM EX270 (270 MHz) or a JEOL JNM GSX500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; m, multiplet. ^{13}C NMR spectra were recorded on a JEOL JNM GSX500 (500 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard ($CDCl_3$; δ 77.0 ppm). High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102A mass spectrometer. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Silica-gel column chromatography was carried out on silica gel 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm). Optical rotations were measured on a Horiba SEPA300 polarimeter. Elemental analyses were carried out on a Yanaco CHN Corder MT-5. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102A mass spectrometer.

4.2. Benzyl 2-oxocyclohexanecarboxylate (8)[21]

A solution of ethyl 2-oxocyclohexanecarboxylate (**7**, 5.01 g, 29.4 mmol) and benzyl alcohol (3.85 g, 35.6 mmol) in toluene (44 mL) was stirred at 120 °C (oil bath temp.) for three days. After evaporation of toluene, the residue was purified by column chromatography on silica gel (hexane-ether = 10/1) to afford **8** (5.64 g, 24.3 mmol, 83%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, a mixture of keto and enol forms (keto/enol = 1:3)) δ : 1.56-1.70 (4H, m, enol), 1.74-1.88 (2H, m, keto), 1.91-1.99 (1H, m, keto), 2.08-2.20 (2H, m, keto), 2.26 (4H, m, enol), 2.30-2.38 (1H, m, keto), 2.45-2.52 (1H, m, keto), 3.42 (1H, ddd, J = 10.0, 5.5, 1.0 Hz, keto), 5.16 (1H, d, J = 12.5 Hz, keto), 5.19 (2H, s, enol), 5.21 (1H, d, J = 12.0 Hz, keto), 7.29-7.44 (5H, m), 12.1 (1H, s, enol OH); ^{13}C NMR (126 MHz, $CDCl_3$) δ : 21.8, 22.3, 22.3, 23.3, 27.0, 29.1, 29.9, 41.5, 57.2, 65.6, 66.7, 97.6, 127.8, 128.0, 128.1, 128.1, 128.2, 128.3, 128.5, 128.5, 129.6, 132.9, 135.6, 136.1, 169.8, 172.3, 172.5, 205.8.

4.3. Benzyl (1*S*,2*R*)-2-{[(1'*R*)-1'-phenylethyl]amino}cyclohexanecarboxylate (9)[8c]

A solution of **8** (4.79 g, 20.6 mmol), (*R*)-phenylethylamine (2.57 mmol, 21.2 mmol), and isobutyric acid (1.9 mL, 20.5 mmol) in toluene (21 mL) was refluxed for 2 h with azeotropic removal of water. This solution was cooled to room temperature, and added to the reducing medium prepared as follows.

To isobutyric acid (57.3 mL, 618 mmol) was added sodium borohydride (2.34 g, 61.9 mmol) portion wise under nitrogen at 0-10 °C. The mixture was stirred at 20 °C for 0.5 h and then cooled to 0 °C. The above-mentioned enamine solution in toluene was added dropwise at 0 °C, and the mixture was stirred for 2 h at 0 °C. The reaction was quenched with water, and the mixture was basified with 10% NaOH solution (pH 9~10). The resulting mixture was extracted with ether, and combined organic extracts were dried with anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane-ethyl acetate = 10:1 to 5:1) to afford a mixture of **9** and diastereomers (5.95 g, 86%, 82% de by ^{1}H NMR analysis) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$, major isomer) δ : 1.17 (3H, d, J = 6.7 Hz), 1.20-1.32 (2H, m), 1.40-1.68 (5H, m), 1.84-1.93 (1H, m), 2.79 (1H, dt, J = 7.3, 3.7 Hz), 2.86 (1H, dt, J = 7.9, 3.7 Hz), 3.78 (1H, q, J = 6.7 Hz), 5.16 (2H, s), 7.13-7.43 (10H, m); ^{1}H NMR (500 MHz, $CDCl_3$, minor isomer) δ : 1.27 (3H, d, J = 6.7 Hz), 2,57 (1H, dt, J = 9.2, 3.7 Hz), 3.85 (1H, t, J = 6.7 Hz), 4.97 (1H, d, J = 12.8 Hz, one of OCH_2Ph); ^{13}C NMR (68 MHz, $CDCl_3$, major isomer) δ : 22.6, 23.2, 24.4, 25.3, 29.7, 44.7, 53.3, 54.9, 65.8, 126.5, 126.6, 128.0, 128.2, 128.5, 136.2, 146.4, 174.2; ^{13}C-NMR (68 MHz, $CDCl_3$, minor isomer) δ : 21.4, 23.9, 24.7, 25.4, 27.6, 46.5, 51.7, 54.2, 65.8, 126.6, 126.7, 128.0, 128.1, 128.4, 136.2, 145.9, 174.3.

4.4. (1*S*,2*R*)-2-Aminocyclohexanecarboxylic acid (5)[8c]

A mixture of **9** and a diastereomer (2.01 g, 5.96 mmol) and 20% $Pd(OH)_2/C$ (210 mg, 0.30 mmol) in MeOH (8 mL) was heated at 50 °C under H_2 atmosphere (50 atm.) for 24 h. Then, the mixture was filtered through Celite pad, and the filtrate was concentrated in vacuo to afford a crude product. The crude product was recrystallized twice from H_2O and acetone to afford **5** (458 mg, 3.20 mmol, 54%, not optimized) as a colorless needles. ^{1}H NMR (270 MHz, D_2O) δ : 1.18-1.42 (3H, m), 1.42-1.60 (2H, m), 1.60-1.72 (2H, m), 1.72-1.90 (1H, m), 2.51 (1H, dt, J = 6.8, 4.1 Hz), 3.33 (1H, td, J = 6.2, 4.3 Hz); ^{13}C NMR (68 MHz, CD_3OD) δ : 23.9, 24.0, 28.0, 28.8, 44.5, 51.8, 180.1; mp 215-220 °C (dec.) (lit. 217-220 °C,[13] 220-223 °C[8c]); $[\alpha]_D^{29}$ = +20.2 (c 0.25, H_2O) (lit.[13] $[\alpha]_D^{24}$ = +20.0 (c 0.25, H_2O)).

HPLC analysis of *N*-Cbz derivative of thus obtained **5** by using chiralcel ODH (hexane/*i*-PrOH/HCO_2H = 95/5/1, 0.5 mL/min, 254 nm) indicated that only (1*S*,2*R*)-enantiomer was included ((1*S*,2*R*)-enantiomer: 13.8 min, (1*R*,2*S*)-enantiomer: 15.3 min).

4.5. (1*S*,2*R*)-2-Phthalimidocyclohexanecarboxylic acid (12)

A mixture of **5** (325.6 mg, 2.27 mmol) and powdered phthalic anhydride (371 mg, 2.50 mmol) was heated at 150 °C for 2 h. The mixture was purified by column chromatography on silica gel (hexane-ethyl acetate = 3:1 to 1:1) gave **12** (552 mg, 89%) and recrystallization with hexane (30 mL) and ethyl acetate (3 mL) gave **12** (465 mg, 1.70 mmol, 75%) as a colorless cubic crystals. ^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.34-1.45 (1H, m), 1.53-1.59 (1H, m), 1.63-1.72 (1H, m), 1.77-1.84 (1H, m), 1.91-2.02 (2H, m), 2.13-2.19 (1H, m), 2.83 (1H, qd, J = 9.3, 3.4 Hz), 3.16 (1H, td, J = 4.6, 3.2 Hz), 4.34 (1H, ddd, J = 12.5, 5.1, 3.4

Hz), 7.66 (2H, dd, *J* = 5.4, 2.9 Hz), 7.77 (2H, dd, *J* = 5.4, 2.9 Hz); ^{13}C NMR (127 MHz, $CDCl_3$) δ : 21.1, 25.9, 25.9, 27.4, 42.8, 52.7, 123.1, 131.9, 133.8, 168.6, 178.0; IR ($CHCl_3$, cm^{-1}) 3020, 1709; mp 159-160 °C; $[\alpha]_D^{28}$ = +98.3 (*c* 1.00, MeOH); Anal. Calcd. for $C_{15}H_{15}NO_4$: C, 65.92; H, 5.53; N, 5.13. Found: C, 65.93; H, 5.56; N, 5.15.

4.6. (1*S*,2*R*)-1-(*N*-Benzyloxycarbonylamino)-2-phthalimidocyclohexane (15)

To a stirred solution of **12** (100 mg, 0.367 mmol) and dimethylformamide (3 drops) in dry CH_2Cl_2 (6 mL) was added thionyl chloride (0.27 mL, 3.70 mmol) at 0 °C, and the mixture was stirred at room temperature for 1 h. After evaporation of volatiles, dry acetone (5 mL) was added to the residue. To this solution was added a saturated aqueous solution of NaN_3 (1 mL) at 0 °C, and the mixture was stirred for 10 min. Excess amount of H_2O was added to the reaction mixture, and the precipitated solid was collected by filtration, and dried in vacuo to give crude acyl azide **14** (102.9 mg).

A mixture of thus-obtained acyl azide **14** (102.9 mg) in dry toluene (3 mL) was refluxed for 1 h. After confirming the disappearance of acyl azide by TLC analysis, benzyl alchohol (0.19 mL, 1.84 mmol) was added and the mixture was refluxed for 27 h. After the addition of H_2O, the mixture was extracted with ethyl acetate, and combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (benzene-ethyl acetate) to afford **15** (108.8 mg, 0.288 mmol, 78%) as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.33-1.53 (2H, m), 1.53-1.73 (3H, m), 1.84-2.13 (2H, m), 2.69 (1 H, qd, *J* = 13.1, 3.3 Hz), 4.03-4.08 (0.1 H, brs), 4.11 (0.9 H, d, *J* = 3.4 Hz), 4.24-4.32 (0.1H, brs), 4.36 (0.9 H, dt, *J* = 13.4, 3.7 Hz), 4.73-4.86 (0.1 H, brs), 4.96 (0.9H, d, *J* = 12.5 Hz), 5.02 (0.9H, d, *J* = 12.5 Hz), 5.65-5.75 (0.1 H, brs), 5.98 (0.9 H, d, *J* = 6.8 Hz), 7.07-7.34 (5 H, m plus brs), 7.68 (2 H, dd, *J* = 5.2, 3.1 Hz), 7.68 (2 H, dd, *J* = 3.1, 5.1 Hz), 7.79 (2 H, dd, *J* = 3.2, 5.2 Hz); ^{13}C NMR (127 MHz, $CDCl_3$) δ : 19.4, 24.3, 25.7, 30.2, 51.1, 52.8, 66.2, 123.2, 127.7, 127.7, 128.3, 131.6, 133.9, 136.7, 156.0, 168.9; IR ($CHCl_3$, cm^{-1}) 1709, 1518; mp 114.0-115.0 °C; $[\alpha]_D^{29}$ = +92.14 (*c* 0.10, MeOH); HRMS (EI) Calculated for $C_{22}H_{22}N_2O_4$: 378.15796. Found 378.15866.

4.6. (1*S*,2*R*)-1-(*N*-Benzyloxycarbonylamino)-2-acetamidecyclohexane (16)

A mixture of **15** (82.4 mg, 0.218 mmol) and 1 M solution of hydrazine in MeOH (2.5 mL) in MeOH (10 mL) was refluxed for 10 h. After evaporation of the solvent, ethyl acetate was added to the residue, and the mixture was washed with water and brine, dried over anhydrous Na_2SO_4, filtered and concentrated in vacuo. To the obtained residue was added pyridine (0.9 mL) and acetic anhydride (3 mL), and the mixture was stirred at room temperature for 2 h. After evaporation of volatiles, ethyl acetate and saturated aqueous $NaHCO_3$ were added. The organic layer was separated, and washed with water and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated. The crude product was purified by preparative thin-layer chromatography on silica gel ($CHCl_3$/MeOH = 9:1) to afford **16** (54.8 mg, 0.189 mmol, 87%) as a colorless solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ : 1.30-2.00 (8 H, m), 1.95 (3H, s), 3.90 (1 H, s), 4.02 (1 H, s), 5.10 (2 H, s), 5.28 (1 H, s), 5.75-5.95 (0.2 H, brs), 6.05-6.23 (0.8 H, brs), 7.30-7.38 (5 H, m); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ : 21.3, 22.6, 23.4, 28.0, 29.2, 50.1, 50.8, 66.9, 128.1, 128.5, 136.3, 156.6, 170.2; IR ($CHCl_3$, cm^{-1}) 1713, 1667; mp 163.0-164.0 °C; $[\alpha]_D^{29}$ = +33.6 (*c* 0.10, MeOH); Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.18; H, 7.64; N, 9.65. Found: C, 66.24; H, 7.66; N, 9.58.

Acknowledgments

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