SYNTHESIS OF (+)- AND (-)-ETHOSUXIMIDES UTILIZING ASYMMETRIC NITROOLEFINATION

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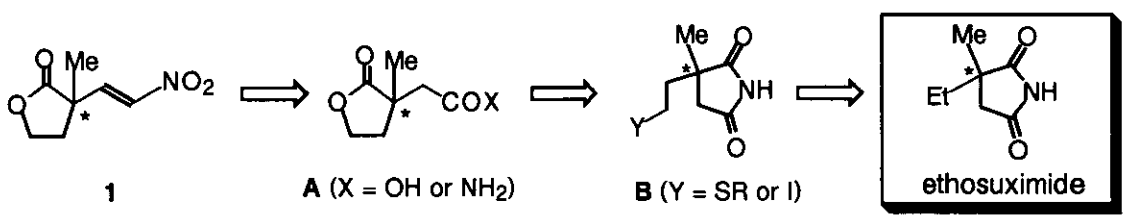
Abstract - Both enantiomers of ethosuximide were synthesized from (*S*)-(-)- and (*R*)-(+)-2-methyl-2-[(*E*)-2-nitroethenyl]-γ-butyrolactones (**1**), which were obtained by asymmetric nitroolefination of α-methyl-γ-butyrolactone, *via* the lactone carboxylic acid (**3**).

Racemic ethosuximide (2-ethyl-2-methylsuccinimide) is commonly used in the treatment of petit mal epilepsy.[1] Although ethosuximide produced the lowest incidence of fatal malformations among six commonly used antiepleptic drugs, the teratogenic activity has been observed on the fetuses of mice by the administration of ethosuximide.[2] The asymmetric synthesis and optical resolution of ethosuximide were not realized yet. Therefore, the relationship of its absolute configuration and specific rotation as well as pharmacological activity is unknown. These facts prompted us to synthesize both enantiomers of ethosuximide.

Racemic ethosuximide has been industrially produced by Knoevenagel condensation of ethyl methyl ketone with ethyl cyanoacetate as a key step.[3] Recently it was synthesized by uncatalyzed cationic olefin cyclization of *N*-vinylic α-chloro-α-thioacetamide.[4] Since ethosuximide has an asymmetric quaternary carbon center, the asymmetric synthesis of quaternary carbon is required for the synthesis of optically active ethosuximide. We have recently developed the asymmetric nitroolefination[5] of α-substituted γ- or δ-lactones through an addition-elimination process to construct an asymmetric quaternary carbon at the α-position of lactone, and applied the methods to natural product syntheses[6]. We report here the asymmetric synthesis of both enantiomers of ethosuximide utilizing an improved asymmetric nitroolefination.[5a,b]

Our synthetic strategy for optically active ethosuximide is outlined in Scheme 1.

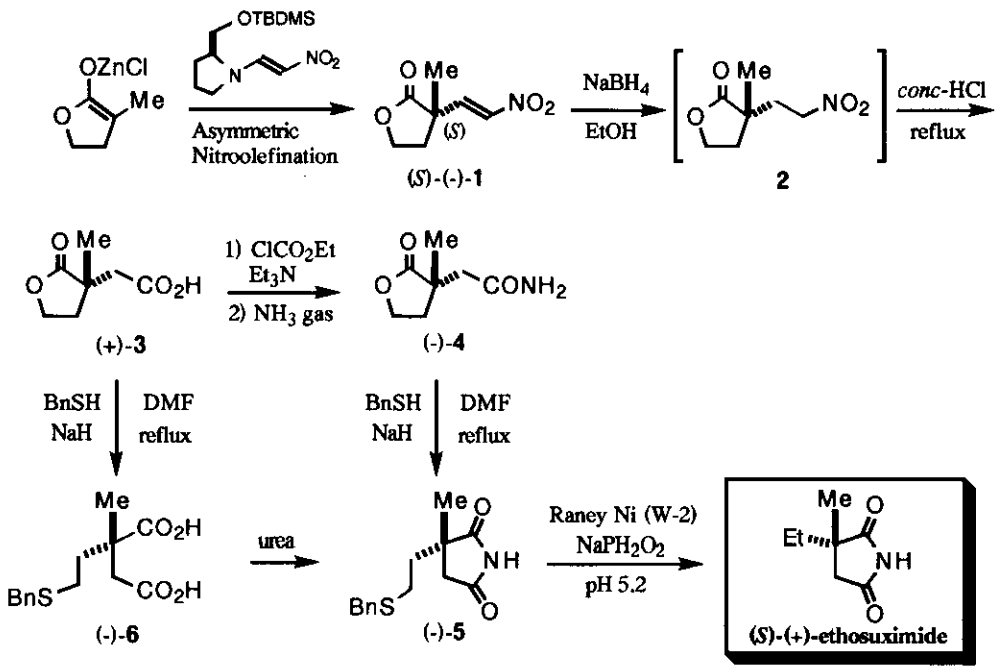
Scheme 1



1 **A** (X = OH or NH_2) **B** (Y = SR or I)

If the nitroethenyl group of optically active 2-methyl-2-(2-nitroethenyl)-γ-butyrolactone (**1**) can be converted to acetic acid moiety, a lactone carboxylic acid (**A**) has a proper carbon skeleton and functional groups for the synthesis of ethosuximide. In order to use the β and γ carbons of γ-butyrolactone as the ethyl substituent in ethosuximide, the lactone ring of carboxylic acid (**A**, X = OH) or its amide derivative (**A**, X = NH_2) should be opened by the C-O bond cleavage with a nucleophile (Y^-) which is able to be reduced, followed by imidation, to give an imide (**B**) which could be led to the optically active ethosuximide by reductive elimination of the Y group. A synthetic route to (*S*)-ethosuximide is shown in Scheme 2.

Scheme 2. An Asymmetric Synthesis of (*S*)-(+)-Ethosuximide



Reduction of nitroolefin [(*S*)-(-)-**1**] (84 %ee), which was prepared by the asymmetric nitroolefination [5a,b] of α-methyl-γ-butyrolactone, to a saturated nitro lactone (**2**) with sodium borohydride or sodium cyanoborohydride was effective, but the isolated yields of **2** after chromatographic purification on silica gel were less than 65 % yield in several trials. Since the low yield is attributable to an absorption of *aci*-nitro form of **2** on silica gel, we tried oxidation[7] of nitromethylene group without purification of **2**. Treatment of the crude reduction product (**2**) with concentrated hydrochloric acid afforded the desired carboxylic acid [(+)-**3**] in 82 % yield (2 steps). The ee of carboxylic acid [(+)-**3**] could be enhanced to 96 %ee by recrystallization from ethyl acetate, which was determined by a chiral HPLC analysis of its methyl ester (see EXPERIMENTAL). The carboxylic acid [(+)-**3**] was led to amide [(-)-**4**] by a mixed anhydride method with ammonia in 83 % yield. In the S_N2 type cleavage of γ-lactone, it was known that the alcoholic carbon of lactone was attacked by thiolate or iodide anion as a nucleophile to give the corresponding sulfide or iodide.[8] Then, we chose phenylmethanethiolate anion as a reagent for the ring opening because of the easiness in selective reduction of the resulting sulfide. The reaction of lactone [(-)-**4**] with sodium

phenylmethanethiolate in DMF at 150 ℃ for 11 h gave imide [(-)-**5**] in 59 % yield, in which dehydration was accompanied. However, the reproducibility of the yield in the above reaction was poor. We attempted an another synthetic route from (+)-**3** to (-)-**5**, in which the lactone was opened before imidation. The γ-lactone opening of (+)-**3** with sodium phenylmethanethiolate gave dicarboxylic acid [(-)-**6**] in 90 % yield. Dicarboxylic acid [(-)-**6**] was converted into imide [(-)-**5**] with urea by heating at 120 ℃ for 8 h in 89 % yield. Reductive desulfurization of (-)-**5** with Raney nickel (W-2) - sodium hypophosphite combination system[9] afforded (*S*)-(+)-ethosuximide {$[\alpha]_D^{25}$ +28.6° (0.47, $CHCl_3$), >99 %ee} in 70 % yield, whereas an independent use of Raney nickel (W-2) gave only trace ethosuximide probably due to its absorption on the nickel surface. Enhancement in the optical purity of (*S*)-(+)-ethosuximide was observed on crystallization of (*S*)-(+)-ethosuximide.

(*R*)-(-)-Ethosuximide {$[\alpha]_D^{24}$ -28.0° (0.83, $CHCl_3$), 97 %ee} was also prepared from (*R*)-(+)-**1** (81 %ee) according to the same procedure described above.

In conclusion, we have synthesized both enantiomers of ethosuximide and established the relationship between the absolute configuration and specific rotation though the configuration was based on a deduced configuration of nitroolefin (**1**) which was determind by comparison of the CD spectra with that of (*S*)-nitroolefin having δ-lactone.[5a]

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EXPERIMENTAL

General: Melting points are taken with a micro hot-stage apparatus (Yanagimoto) and are uncorrected. IR spectra were recorded with a JASCO IR-810 diffraction grating infrared spectrophotometer. ^{1}H-NMR spectra were obtained with a Varian XL-300 NMR spectrometer. Signals are given in ppm using tetramethylsilane as an internal standard. MS spectra were determined on a JEOL JMS SX-102A QQ. Specific rotations were recorded on a Horiba SEPA-200 polarimeter in the indicated solvent. Combustion analyses were performed by a Yanaco CHN-corder MT-3. Wakogel C-200 (100-200 mesh, Wako Pure Chemical) was used for open-column chromatography. Kieselgel 60 Art. 9385 (Merck) and silica gel 60H (nacalai tesque) were used for flash column chromatography. Kieselgel 60 F_{254} plates (Merck) was used for thin layer chromatography (TLC). Preparative TLC (PTLC) was done with Kieselgel 60 F_{254} plates (0.25 mm, Merck). If necessary, compounds were purified by a recycle HPLC (LC-908, Japan Analytical Industry Co., Ltd.) on GPC columns (JAIGEL 1H and 2H) after purification on silica gel.

Materials: DME and ether were distilled from sodium benzophenone ketyl under a nitrogen atmosphere before use. Diisopropylamine, triethylamine, and DMF were distilled from calcium hydride under a nitrogen atmosphere before use.

(*S*)-(-)- and (*R*)-(+)-2-Methyl-2-[(*E*)-2-nitroethenyl]-4-butanolides [(*S*)-(-)-**1** and (*R*)-(+)-**1**] were prepared according to procedure of ref. 5a,b.

(*S*)-(+)-2-Carboxymethyl-2-methyl-4-butanolide [(*S*)-(+)-(3)]

To an ethanol solution (15 mL) of (*S*)-(-)-2-methyl-2-[(*E*)-nitroethenyl]-4-butanolide [(*S*)-(-)-**1**] (84 %ee)

(1.76 g, 10.3 mmol) was added portionwise sodium borohydride (427 mg, 11.2 mmol) at rt, and the reaction mixture was stirred for 15 min. The mixture was quenched with 1 % hydrochloric acid (10 mL), then extracted with ethyl acetate (30 mL x 3). The organic layer was washed with brine (10 mL x 3), dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo*. The crude of **2** (1.61 g) was heated to reflux in *conc.*-hydrochloric acid (8 mL) at 120 °C for 2 d. The mixture was diluted with water (20 mL), then the aqueous layer was extracted with ethyl acetate (30 mL x 5). The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The resulting solid was crystallized from ethyl acetate to yield (*S*)-(+)-(**3**) (1.34 g, 82 %). After additional five times recrystallization were performed to enrich the optical purity, in which the each first crops were discarded because of their low optical purity (see the section of Determination of Optical Purity), optical purity enriched (96 %ee) (*S*)-(+)-(**3**) (980 mg) was obtained as colorless crystals. (*S*)-(+)-(**3**): mp 105-107 °C; $[\alpha]_D^{18}$ +2.63° (c 1.40, $CHCl_3$) (96 %ee); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 2.12 (dd of ABd, J_{AB} = 12.8 Hz, J = 7.3 and 3.1 Hz, 1H), 2.49 (t of ABd, J_{AB} = 12.8 Hz, J = 9.2 Hz, 1H), 2.68 (ABd, J_{AB} = 17.1 Hz, 1H), 2.80 (ABd, J_{AB} = 17.1 Hz, 1H), 4.30 (dd of ABd, J_{AB} = 9.2 Hz, J = 9.2 and 7.3 Hz, 1H), 4.40 (dd of ABd, J_{AB} = 9.2 Hz, J = 9.2 and 3.1 Hz, 1H); IR ($CHCl_3$): 2995 (br), 1770, 1720, 1400, 1260, 1170, 1090, 1030 cm^{-1}; MS (FAB): *m/z* 159 (M^++1, 14); HRMS calcd for $C_7H_{11}O_4$ (M^++1): 159.0657, found: 159.0657; Anal. Calcd for $C_7H_{10}O_4$: C; 53.16, H; 6.37. Found: C; 53.19, H; 6.52.

(*R*)-(-)-(**3**) was prepared from [(*R*)-(+)-**1**] (81 %ee) on the same procedure described above. (*R*)-(-)-(**3**): $[\alpha]_D^{17}$ -2.20° (c 2.00, $CHCl_3$) (94 %ee).

In the preliminary experiment using racemic nitroolefin (**1**), the purification of the reduced product by silica gel column chromatography gave an analytical sample of 2-methyl-2-nitroethyl-4-butanolide (**2**); mp 20-25 °C (hexane); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 3H), 2.13 (dd of ABd, J_{AB} = 12.9 Hz, J = 7.0 and 5.1 Hz, 1H), 2.21 (t of ABd, J_{AB} = 12.9 Hz, J = 7.9 Hz, 1H), 2.31 (dd of ABd, J_{AB} = 14.4 Hz, J = 8.9 and 6.6 Hz, 1H), 2.40 (dd of ABd, J_{AB} = 14.4 Hz, J = 8.8 and 6.3 Hz, 1H), 4.27-4.40 (m, 2H), 4.53 (dd of ABd, J_{AB} = 13.7 Hz, J = 8.8 and 6.6 Hz, 1H), 4.62 (dd of ABd, J_{AB} = 13.7 Hz, J = 8.9 and 6.3 Hz, 1H); IR ($CHCl_3$): 2990, 2920, 1770, 1555, 1455, 1430, 1385, 1370, 1180, 1100, 1030 cm^{-1}; MS (FAB) *m/z* 174 (M^++1, 93); HRMS calcd for $C_7H_{12}NO_4$ (M^++1): 174.0766, found. 174.0753; Anal. Calcd for $C_7H_{11}NO_4$: C, 48.55; H, 6.40; N, 8.09. Found: C, 48.50; H, 6.47; N, 8.04.

Determination of Optical Purity of Carboxylic Acid (3)

Both enantiomers of carboxylic acid (**3**) were converted into their methyl esters with diazomethane in ether at 0° C. methyl ester of **3**: pale yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 2.11 (dd of ABd, J_{AB} = 12.8 Hz, J = 7.4 and 3.4 Hz, 1H), 2.48 (t of ABd, J_{AB} = 12.8 Hz, J = 9.0 Hz, 1H), 2.62 (ABd, J_{AB} = 16.7 Hz, 1H), 2.73 (ABd, J_{AB} = 16.7 Hz, 1H), 3.70 (s, 3H), 4.29 (dd of ABd, J_{AB} = 9.0 Hz, J = 9.0 and 7.4 Hz, 1H), 4.39 (dd of ABd, J_{AB} = 9.0 Hz, J = 9.0 and 3.4 Hz, 1H); IR ($CHCl_3$): 2990, 2950, 2910, 1765, 1735, 1435, 1380, 1355, 1160, 1085, 1025 cm^{-1}; MS *m/z*: 172 (M^+, 3), 157 (2), 141 (29), 128 (6), 113 (9), 99 (33), 96 (53), 85 (11), 69 (100), 68 (88); HRMS calcd for $C_8H_{12}O_4$: 172.0735, found: 172.0744.

The optical purity of **3** was determined by a chiral HPLC analysis (a Daicel CHIRALPAK AS column (25 x 0.46, eluent; hexane : *i*-PrOH = 9 : 1, flow rate; 1.0 mL/min, Temp; 25 °C, detector; 230 nm) using methyl esters of **3**. methyl ester of (-)-**3**: 19 min; methyl ester of (+)-**3**: 24 min).

(*S*)-(-)-2-Carbamoylmethyl-2-methyl-4-butanolide [(*S*)-(-)-4]

To a chloroform (3 mL) solution of (*S*)-(+)-(**3**) (102 mg, 0.64 mmol) were added successively

triethylamine (0.18 mL, 1.3 mmol) and ethyl chloroformate (0.12 mL, 1.3 mmol) at 0 °C. After the mixture was stirred for 1 h, ammonia gas was introduced to the reaction mixture at 0 °C for 5 min, then the reaction mixture was stirred at rt for an additional 1 h. After condensation of the solvent *in vacuo*, the crude material was purified by silica gel column chromatography (eluent: ethyl acetate) to give (*S*)-(-)-**4** (84 mg, 83 %). (*S*)-(-)-**4**: mp 116-118 °C (hexane / ethyl acetate); $[\alpha]_D^{21}$ -18.8° (c 0.96, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 2.12 (dd of ABd, J_{AB} = 12.9 Hz, J = 7.1 and 3.2 Hz, 1H), 2.48 (ABd, J_{AB} = 14.8 Hz, 1H), 2.56 (t of ABd, J_{AB} = 12.9 Hz, J = 9.2 Hz, 1H), 2.64 (ABd, J_{AB} = 14.8 Hz, 1H), 4.30 (dd of ABd, J_{AB} = 9.2 Hz, J = 9.2 and 7.1 Hz, 1H), 4.39 (dd of ABd, J_{AB} = 9.2 Hz, J = 9.2 and 3.2 Hz, 1H), 5.47 (br s, 1H), 5.86 (br s, 1H); IR ($CHCl_3$): 3520, 3430, 3000, 1765, 1690, 1600, 1405, 1390, 1280, 1170, 1100, 1030 cm^{-1}; MS *m/z* 157 (M^+, 4), 140 (9), 112 (11), 99 (32), 59 (100), 55 (48), 44 (65); HRMS calcd for $C_7H_{11}NO_3$: 157.0739, found: 157.0726; Anal. Calcd for $C_7H_{11}NO_3$: C, 53.49; H, 7.05; N, 8.91. Found: C, 53.66; H, 7.17; N, 8.76.

(*R*)-(+)-**4** was prepared from [(*R*)-(-)-**3**] on the same procedure described above. (*R*)-(+)-**4**: $[\alpha]_D^{21}$ +18.1° (c 1.02, $CHCl_3$).

(*S*)-(-)-2-Benzylthioethyl-2-methylbutanedionic Acid [(*S*)-(-)-6]

To a suspension of sodium hydride (60 % in mineral oil, 529.9 mg, 13.25 mmol) in dry DMF (20 mL), which was washed with dry ether (4 mL), was added phenylmethanethiol (1.55 mL, 13.25 mmol) at 0 °C under nitrogen atmosphere. After the evolution of hydrogen gas ceased (*ca.* 15 min), a DMF (5 mL) solution of 2-carboxymethyl-2-methyl-4-butanolide [(*S*)-(+)-(**3**)] (698 mg, 4.42 mmol) was added to the reaction mixture at 0 °C, and then the resultant mixture was heated to reflux at 150 °C for 18 h. The mixture was quenched with 10 % hydrochloric acid (15 mL), then extracted with ether (20 mL x 5). The organic layer was washed with brine (10 mL x 3), dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. Purification of the crude product by silica gel column chromatography (eluent, hexane : ethyl acetate = 4 : 1) and recrystallization from hexane / ethyl acetate gave (*S*)-(-)-**6** (1.12 g, 90 %) as colorless crystals. mp 54-55 °C; $[\alpha]_D^{26}$ -1.97° (c 0.82, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.26 (s, 3H), 1.76-2.00 (m, 2H), 2.35-2.42 (m, 2H), 2.43 (ABd, J_{AB} = 17.0 Hz, 1H), 2.78 (ABd, J_{AB} = 17.0 Hz, 1H), 3.71 (s, 2H), 7.23-7.31 (m, 5H); IR ($CHCl_3$): 3050, 2975, 2925, 1710, 1600, 1450, 1410, 920 cm^{-1}; MS (FAB): *m/z* 283 (M^++1, 9); HRMS calcd for $C_{14}H_{19}O_4S$ (M^++1): 283.1004, found: 283.1014.

(*R*)-(+)-**6** was prepared from [(*R*)-(-)-**3**] on the same procedure described above. (*R*)-(+)-**6**: $[\alpha]_D^{25}$ +1.85° (c 1.05, $CHCl_3$).

(*R*)-(-)-2-Benzylthioethyl-2-methylsuccinimide [(*R*)-(-)-5]

(Method A): To a suspension of sodium hydride (60 % in mineral oil, 94.9 mg, 2.4 mmol) in dry DMF (1 mL), which was washed with dry hexane (15 mL), was added phenylmethanethiol (148 mg, 1.2 mmol) at rt under nitrogen atmosphere. After the evolution of hydrogen gas ceased (*ca.* 15 min), a DMF (4 mL) solution of (*S*)-(-)-2-carbamoylmethyl-2-methyl-4-butanolide [(*S*)-(-)-**4**] (62.1 mg, 0.40 mmol) was added to the reaction mixture at rt, and then the resultant mixture was heated to reflux at 150 °C for 11 h. The mixture was poured into saturated ammonium chloride solution, then extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent, hexane : ethyl acetate = 15 : 1) to give (*R*)-(-)-**5** (61 mg, 59 %).

(Method B): A mixture of 2-benzylthioethyl-2-methylbutanedionic acid [(*S*)-(-)-**6**] (1.12 g, 3.96 mmol) and urea (476 mg, 7.93 mmol) was heated at 130 °C for 8 h. Purification by silica gel column chromatography

(eluent, hexane : ethyl acetate = 1 : 1) of the crude product and recrystallization from hexane / ethyl acetate gave (*R*)-(-)-**5** (932 mg, 89 %) as colorless crystal. mp 82-84 °C; $[\alpha]_D^{17}$ -2.20° (c 2.00, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.29 (s, 3H), 1.81 (dd of ABd, J_{AB} = 14.0 Hz, J = 10.6 and 5.3 Hz, 1H), 1.95 (dd of ABd, J_{AB} = 14.0 Hz, J = 10.6 and 5.8 Hz, 1H), 2.32 (dd of ABd, J_{AB} = 12.9 Hz, J = 10.6 and 5.8 Hz, 1H), 2.43 (ABd, J_{AB} = 18.5 Hz, 1H), 2.44 (dd of ABd, J_{AB} = 12.9 Hz, J = 10.6 and 5.3 Hz, 1H), 2.62 (ABd, J_{AB} = 18.5 Hz, 1H), 3.71 (s, 2H), 7.23-7.40 (m, 5H), 7.90 (br s, 1H); IR ($CHCl_3$): 3390, 3190, 3050, 2920, 1780, 1720, 1485, 1445, 1375, 1340, 1300, 1180, 1130, 1095 cm^{-1}; MS *m/z* 263 (M^+, 28), 172 (14), 151 (18), 123 (19), 113 (29), 91 (100); HRMS calcd for $C_{14}H_{17}NO_2S$: 263.0980, found: 263.0985.

(*S*)-(+)-**5** was prepared from [(*R*)-(+)-**6**] on the same procedure described above. (*S*)-(+)-**5**: $[\alpha]_D^{18}$ +2.63° (c 1.40, $CHCl_3$).

(*S*)-(+)-2-Ethyl-2-methylsuccinimide [(*S*)-(+)-Ethosuximide]

To a solution of (*R*)-(-)-2-benzylthioethyl-2-methylsuccinimide [(*R*)-(-)-**5**] (61.3 mg, 0.23 mmol) in an acetate buffer (pH 5.2) and ethanol (1 : 2, 9 mL) was added freshly prepared Raney Ni (W-2) (suspension in ethanol, 5 mL), followed by the addition of sodium hypophosphite monohydrate (321 mg, 3.0 mmol, in 2 mL water solution) immediately, and the resultant solution was stirred for 0.5 h at rt. The reaction mixture was filtered with celite and washed with hot methanol, then concentrated *in vacuo*. The residue was poured into 1 % hydrochloric acid, then the mixture was extracted with ethyl acetate (10 mL x 5). The organic layer was washed with brine (5 mL x 3), dried over anhydrous magnesium sulfate, filtered, concentrated *in vacuo*. Purification by silica gel column chromatography (hexane : ethyl acetate = 2:1) of the crude product and recrystallization from hexane / ethyl acetate gave (*S*)-(+)-ethosuximide (23.1 mg, 70 %) as colorless needles. mp 60-61 °C; $[\alpha]_D^{25}$ +28.6° (c 0.47, $CHCl_3$); >99 %ee {determined by a chiral HPLC analysis [a Daicel CHIRALCEL OJ column (25 x 0.46, eluent; hexane : *i*-PrOH = 9 : 1, flow rate; 1.0 mL/min, Temp; 25 °C, detector; 254 nm, (*S*)-(+)-ethosuximide: 12 min, (*R*)-(-)-ethosuximide: 15 min. No peak was observed at the retention time (15 min) for (*R*)-(-)-ethosuximide under the condition of maximun sensitivity.}; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.93 (t, J = 7.5 Hz, 3H), 1.32 (s, 3H), 1.61 (q of ABd, J_{AB} = 13.9 Hz, J = 7.5 Hz, 1H), 1.75 (q of ABd, J_{AB} = 13.9 Hz, J = 7.5 Hz, 1H), 2.47 (ABd, J_{AB} = 18.4 Hz, 1H), 2.67 (ABd, J_{AB} = 18.4 Hz, 1H), 8.35 (br s, 1H); IR ($CHCl_3$): 3400, 3200, 3080, 2970, 2940, 1780, 1720, 1495, 1455, 1375, 1350, 1300, 1265, 1120, and 1040 cm^{-1}; MS (FAB) *m/z* 142 (M^++1, 34); HRMS calcd for $C_7H_{12}NO_2$ (M^++1): 142.0868, found: 142.0855; Anal. Calcd for $C_7H_{11}NO_2$: C, 59.31; H, 7.91; N, 9.83. Found: C, 59.56; H, 7.85; N, 9.92.

(*R*)-(-)-Ethosuximide was prepared from [(*S*)-(+)-**5**] on the same procedure described above. (*R*)-(-)-Ethosuximide: mp 59-62 °C (ethyl acetate / hexane); $[\alpha]_D^{24}$ -28.0° (c 0.83, $CHCl_3$); 97 %ee {determined by chiral HPLC analyses [a Daicel CHIRALCEL OJ column (25 x 0.46, eluent; hexane : *i*-PrOH = 9 : 1, flow rate; 1.0 mL/min, Temp; 25 °C, detector; 254 nm, (*S*)-(+)-ethosuximide: 12 min, (*R*)-(-)-ethosuximide: 15 min}.

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