A NEW DIVERGENT ASYMMETRIC SYNTHESIS OF (+)- AND (-)-ETHOSUXIMIDES AND THEIR ANTI-CONVULSANT ACTIVITIES

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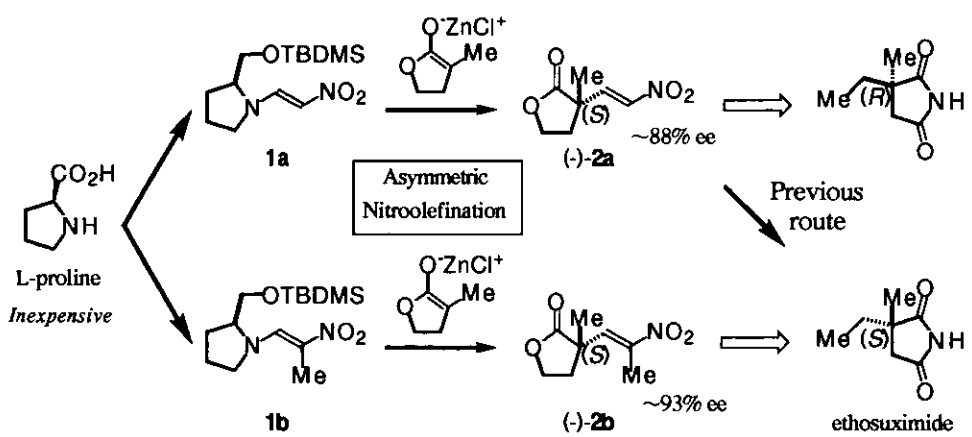
Abstract - Both enantiomers of ethosuximide were synthesized divergently from nitroolefin lactone [(-)-**2a**] or [(-)-**2b**], which was obtained by asymmetric nitroolefination of α-methyl-γ-butyrolactone with chiral nitro enamines derived from L-proline. Although anticonvulsant activity was confirmed in both enantiomers, the (*S*)-ethosuximide was more active than the (*R*)-enantiomer.

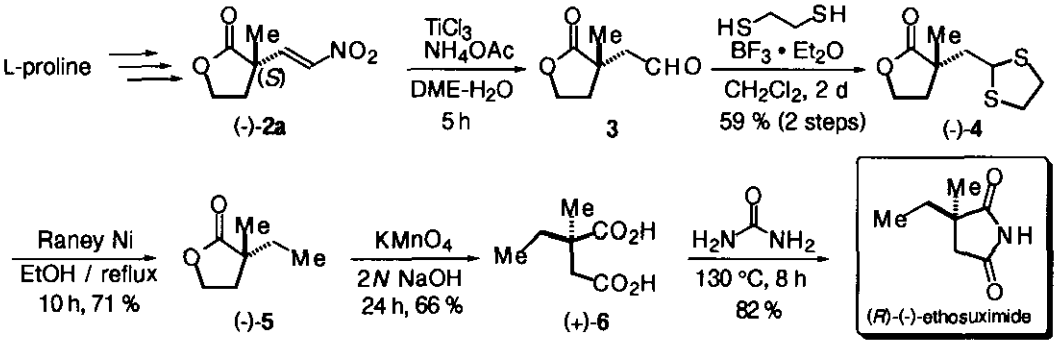
As part of our program for the development of an enantioselective carbon-carbon bond forming reaction to create an asymmetric quaternary carbon through an addition-elimination process using readily available chiral nitro enamines,[1,2] we have synthesized[3] both enantiomers of ethosuximide[4] (2-ethyl-2-methylsuccinimide) which are commonly used as a racemic form in the treatment of petit mal epilepsy.[5] In the above synthesis, the *R*- and *S*-enantiomers were obtained by the asymmetric nitroolefination of α-methyl-γ-lactone using the chiral nitro enamines derived from D- and L-prolines, respectively. This asymmetric synthesis has the disadvantage of requiring use of an expensive D-proline, especially in a large-scale synthesis. In order to overcome this drawback, we studied a new synthetic route for the *R*-enantiomer from a chiral nitro enamine derived from inexpensive L-proline. Here we report a divergent synthesis of both enantiomers of ethosuximide from L-proline as well as their bioassay to anticonvulsant activity.

Scheme 1. Synthetic Strategy for Both Enantiomers of Ethosuximide from L-Proline



Our synthetic strategy for both enantiomers of ethosuximide is outlined in Scheme 1. In the previous synthetic route, the nitroolefin moiety of optically active 2-methyl-2-(2-nitroethenyl)-γ-butyrolactone [(-)-**2a**] was converted into an acetic acid moiety and the β and γ carbons of γ-butyrolactone were used as the ethyl substituent in ethosuximide.[3] Therefore, (*S*)-nitroolefin lactone [(-)-**2a**] gave (*S*)-ethosuximide. If the nitroethenyl group can be reduced to the ethyl substituent and the β and γ carbons of γ-butyrolactone can be oxidized to an acetic acid moiety, (*S*)-nitroolefin lactone [(-)-**2a**] would give (*R*)-ethosuximide. Thus, the reverse use of the two different C-2 units on (*S*)-nitroolefin lactone [(-)-**2a**] could lead to the divergent synthesis of both enantiomers of ethosuximide from the same intermediate [(-)-**2a**] derived from L-proline. Furthermore, the conversion of the 2-nitropropenyl group in optically active (*S*)-2-methyl-2-(2-nitropropenyl)-γ-butyrolactone [(-)-**2b**] into an acetic acid moiety *via* the haloform reaction of the derived methyl ketone would be an alternative route for (*S*)-ethosuximide, since the asymmetric nitroolefination of α-methyl-γ-lactone with tri-substituted nitro enamine (**1b**) gave better enantiomeric excess than that with di-substituted nitro enamine (**1a**).[1a] A new synthetic route to (*R*)-ethosuximide from (*S*)-nitroolefin lactone [(-)-**2a**] is shown in Scheme 2.

Scheme 2. Asymmetric Synthesis of (*R*)-(-)-Ethosuximide from Di-substituted Nitroolefin Lactone [(-)-**2a**]

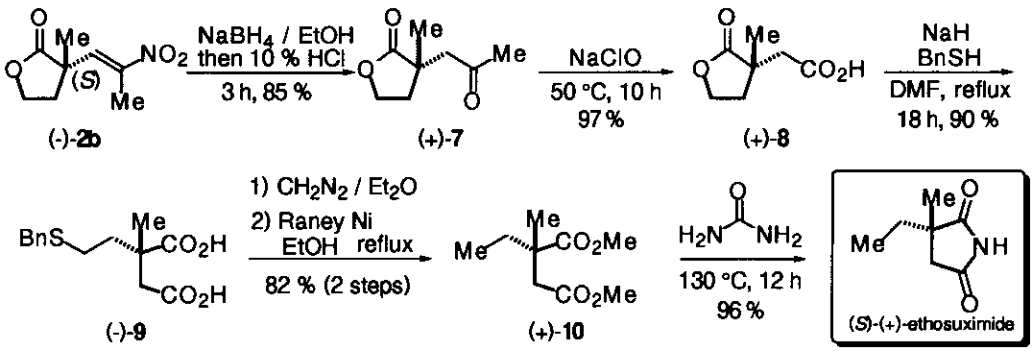


Reductive Nef reaction of nitroolefin [(-)-**2a**], prepared by the asymmetric nitroolefination[1a,b] of α-methyl-γ-butyrolactone, to the aldehyde (**3**) with titanium trichloride and subsequent dithioacetalization with ethanedithiol afforded dithioacetal [(-)-**4**]. The dithioacetal moiety was reductively desulfurized to an ethyl substituent with Raney nickel. Thus, the nitroethenyl group could be reduced to the ethyl substituent on (*R*)-ethosuximide. The remaining manipulation was the oxidation of the γ carbon of γ-butyrolactone [(-)-**5**] to an acetic acid moiety; therefore, γ-butyrolactone [(-)-**5**] was subjected to potassium permanganate oxidation under basic conditions to give the dicarboxylic acid [(+)-**6**], which was subsequently converted in high yield into the desired (*R*)-ethosuximide with urea by heating. The obtained (*R*)-ethosuximide showed 88% ee by a chiral HPLC analysis[3] using a Daicel CHIRALCEL OJ, whose optical purity was enhanced by repeated recrystallization. Thus, we were able to circumvent the drawback of the previous synthesis[3] of (*R*)-ethosuximide using expensive D-proline.

Next, we turned our efforts to the conversion of (-)-**2b** synthesized from **1b** to (*S*)-(+)-ethosuximide, as shown in Scheme 3. Optical purity of (-)-**2a** obtained by asymmetric nitroolefination is less than 88% as above mentioned. So, considerable enantiomeric enhancement by recrystallization is required to get

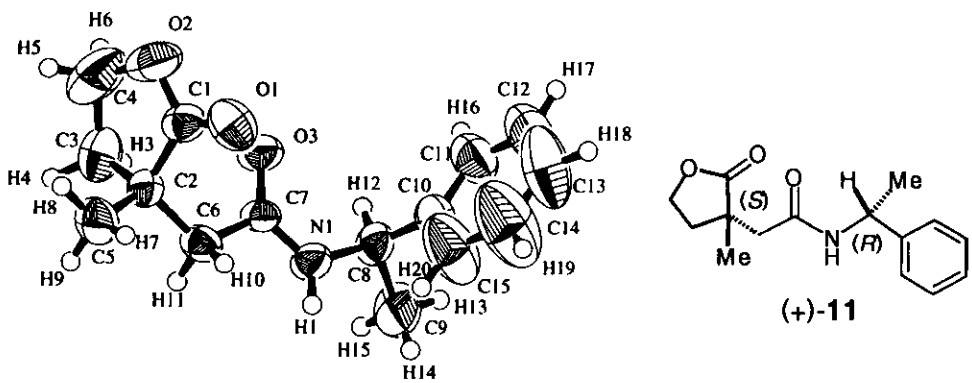
optically pure ethosuximide. Therefore, we planned the use of (-)-**2b** having higher optical purity (up to 93% ee)[1a] for the synthesis of (*S*)-ethosuximide.

Scheme 3. Asymmetric Synthesis of (*S*)-(+)-Ethosuximide from Tri-substituted Nitroolefin Lactone [(-)-**2b**]



Reduction of nitroolefin [(-)-**2b**] with sodium borohydride, and subsequent Nef reaction with hydrochloric acid gave the methyl ketone [(+)-**7**] in high yield. The methyl ketone [(+)-**7**] was led to the carboxylic acid [(+)-**8**] quantitatively by haloform reaction with aqueous sodium hypochlorite. Although the absolute configuration of γ-lactone [(-)-**2b**] has been presumed by comparison of its CD spectrum with that of the corresponding δ-lactone,[1a] the absolute configuration (*S*) of (+)-**8** (98% ee)[6] was determined by an X-Ray crystallographic analysis of an amide [(+)-**11**] shown in Figure 1, which was prepared by the condensation with (*R*)-1-phenylethylamine using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) as a dehydrating agent.

Figure 1



The alcoholic carbon-oxygen bond cleavage reaction[7] of lactone carboxylic acid [(+)-**8**] with sodium benzyl mercaptide in DMF gave dicarboxylic acid [(-)-**9**] in high yield. Attempted reductive desulfurization of diacid (**9**) with Raney nickel failed to give the desired product in high yield; however, its dimethyl ester was desulfurized effectively with Raney nickel. The desired (*S*)-ethosuximide was obtained in high yield by imidation of [(+)-**10**] with urea under heating.

Finally, we tested the anticonvulsant activity of the synthesized (*S*)- and (*R*)-ethosuximides to mice treated with metrazol (pentylenetetrazol), because ethosuximide is known to antagonize the action of metrazol.[8] The results were summarized in Table 1.

Table 1. Anticonvulsant Activity of (+)- and (-)-Ethosuximides to Mice Treated with Metrazol

	Dose (mg/kg, i.v.)	CS / n (%)[a]	TE / n (%)[b]	Died / n (%)[c]
Saline		9 / 9 (100)	9 / 9 (100)	7 / 9 (78)
(*S*)-(+)-ethosximide	80	8 / 9 (89)	6 / 9 (67)	4 / 9 (44)
	120	4 / 9 (44)	3 / 9 (33)	2 / 9 (22)
(*R*)-(-)-ethosximide	80	9 / 9 (100)	6 / 9 (67)	5 / 9 (56)
	120	7 / 9 (78)	4 / 9 (44)	3 / 9 (33)

n; number of mice used. a) CS; number of mice showed clonic seizure b) TE; number of mice showed tonic extension of hind limbs; c) Died; number of mice died

We found that (*S*)-ethosuximide was more active than (*R*)-ethosuximide to mice treated with metrazol in a dose of 120 mg/kg, although both enantiomers have anticonvulsant activity.

ACKNOWLEDGMENT

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EXPERIMENTAL

General: Melting points were taken with a micro hot-stage apparatus (Yanagimoto) or a capillary melting point apparatus (Mitamura Riken) and are uncorrected. IR spectra were recorded with a JASCO IR-810 or Shimadzu FT-IR 8300 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) were 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: Dimethoxyethane (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*)-2-Methyl-2-[(*E*)-2-nitroethenyl]-4-butanolide [(-)-**2a**] and (*S*)-2-Methyl-2-[(*E*)-2-nitropropenyl]-4-butanolide [(-)-**2b**] were prepared according to procedure of ref. 1a,b.

(*S*)-(-)-2-Methyl-2-(2,2-ethylenedithioethyl)-4-butanolide [(-)-4]

To a solution of 1,2-dimethoxyethane (144 mL) and distilled water (104 mL) were added 20% titanium trichloride solution (52.3 mL, 81.0 mmol) and ammonium acetate (38.0 g, 493 mmol) at 0 °C, then the mixture was stirred at rt for 1 h. A 1,2-dimethoxyethane solution (15 mL) of (*S*)-2-methyl-2-[(*E*)-2-nitroethenyl]-4-butanolide [(-)-**2a**] (2.31 g, 13.5 mmol) was added to the reaction mixture at 0 °C, then the resultant mixture was stirred at rt for the additional 5 h. The reaction mixture was quenched with 10% hydrochloric acid (20 mL) then extracted with ethyl acetate (20 mL x 10). The organic layer was washed with brine (15 mL x 2), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo* to give a crude (**3**) (2.34 g). **3**: yellow oil; ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.34 (s, 3H), 2.13 (dd of ABd, J_{AB} = 12.7 Hz, J = 7.3 and 3.3 Hz, 1H), 2.37 (t of ABd, J_{AB} = 12.7 Hz, J = 9.0 Hz, 1H), 2.85 (s, 2H), 4.28-4.47 (m, 2H), 9.75 (s, 1H).

To a dichloromethane solution (50 mL) of the above crude aldehyde (**3**) were added boron trifluoride etherate (0.170 mL, 1.35 mmol) and ethanedithiol (1.40 mL, 16.2 mmol) at 0 °C then the resultant mixture was stirred for 2 d. The reaction mixture was diluted with distilled water (50 mL) then extracted with ethyl acetate (20 mL x 4). The organic layer was washed with brine (15 mL x 3), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by silica gel column chromatography (eluent; hexane : ethyl acetate = 3 : 1) of the residue and recrystallization from hexane / ethyl acetate gave (-)-**4** (1.74 g, 59%) as white powder. (-)-**4**: mp 60-61 °C; $[\alpha]_D^{22}$ -6.28° (*c* 0.35, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.31 (s, 3H), 2.09 (dd of ABd, J_{AB} = 12.9 Hz, J = 8.9 and 4.8 Hz, 1H), 2.17 (d of ABd, J_{AB} = 14.7 Hz, J = 7.9 Hz, 1H), 2.31 (d of ABd, J_{AB} = 14.7 Hz, J = 5.7 Hz, 1H), 2.45 (t of ABd, J_{AB} = 12.9 Hz, J = 7.8 Hz, 1H), 3.18-3.33 (m, 4H), 4.27 (t of ABd, J_{AB} = 8.9 Hz, J = 7.8 Hz, 1H), 4.33 (dd of ABd, J_{AB} = 8.9 Hz, J = 8.9 and 4.8 Hz, 1H), 4.57 (dd, J = 7.9 and 5.7 Hz, 1H); IR ($CHCl_3$): 2990, 2930, 1765, 1600, 1455, 1385, 1370, 1170, 1090, 1025 cm^{-1}; MS (FAB) *m/z* 219 (M^++H, 5); HRMS (FAB) calcd for $C_9H_{15}O_2S_2$ (M^++H) 219.0513, found: 219.0525.

(*R*)-(-)-2-Ethyl-2-methyl-4-butanolide [(-)-5]

To an ethanol solution (30 mL) of (*S*)-2-methyl-2-(2,2-ethylenedithioethyl)-4-butanolide [(-)-**4**] (982 mg, 4.50 mmol) was added freshly prepared Raney nickel (W-2) (suspension in ethanol, 7 mL), then the suspension was refluxed for 10 h. Raney nickel was filtered on celite and washed with hot methanol, then the combined filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (eluent; hexane : ethyl acetate = 3 : 1) to give (-)-**5** (409 mg, 71%). (-)-**5**: pale yellow oil; $[\alpha]_D^{24}$ -15.9° (*c* 0.97, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.95 (t, J = 7.5 Hz, 3H), 1.24 (s, 3H), 1.63 (q, J = 7.5 Hz, 2H), 1.90 (t of ABd, J_{AB} = 12.9 Hz, J = 7.2 Hz, 1H), 2.31 (t of ABd, J_{AB} = 12.9 Hz, J = 7.2 Hz, 1H), 4.26 (t, J = 7.2 Hz, 2H); IR ($CHCl_3$): 2960, 2940, 1765, 1720, 1600, 1260, 1025 cm^{-1}; MS (FAB) *m/z* 128 (M^++H, 34); HRMS (FAB) calcd for $C_7H_{13}O_2$ (M^++H) 128.0837, found: 128.0835. Anal. Calcd for $C_7H_{12}O_2$: C, 65.60; H, 9.44. Found: C, 65.81; H, 9.27.

(*R*)-(+)-2-Ethyl-2-methyl-1,4-butanedioic Acid [(+)-6]

To a 2*N* sodium hydroxide solution (10 mL) of (-)-**5** (121 mg, 0.944 mmol) was added 1*N* potassium permanganate (14.0 mL, 14.0 mmol) at 0 °C, and the mixture was stirred at rt for 24 h. Ethanol (4.0 mL) was added to the reaction mixture, then the resultant precipitate was filtered on celite and washed with ethanol and water. Ethanol was evaporated from the filtrate under reduced pressure. The resultant aqueous solution was acidified with 10% hydrochloric acid (2 mL), then extracted with ethyl acetate (15 mL x 5). The organic layer was washed with brine (5 mL x 2), dried over anhydrous magnesium sulfate, filtered,

and concentrated *in vacuo*. The resultant solid was recrystallized from ethyl acetate to give (+)-**6** (100 mg, 66%) as colorless crystalline. (+)-**6**: mp 101-102 °C; $[\alpha]_D^{24}$ +0.36° (c 0.55, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.92 (t, J = 7.5 Hz, 3H), 1.30 (s, 3H), 1.62 (q of ABd, J_{AB} = 13.8 Hz, J = 7.5 Hz, 1H), 1.71 (q of ABd, J_{AB} = 13.8 Hz, J = 7.5 Hz, 1H), 2.43 (ABd, J_{AB} = 17.1 Hz, 1H), 2.87 (ABd, J_{AB} = 17.1 Hz, 1H); IR ($CHCl_3$): 2970, 2940, 1710, 1460, 1410 cm^{-1}; MS (FAB) *m/z* 161 (M^++H, 26); HRMS (FAB) calcd for $C_7H_{13}O_4$ (M^++H) 161.0813, found: 161.0823.

(*R*)-(-)-2-Ethyl-2-methylsuccinimide [(*R*)-(-)-ethosuximide][3,4d]

A mixture of (+)-**6** (50.0 mg, 0.312 mmol) and urea (188 mg, 3.12 mmol) was heated at 130 °C for 8 h. Purification of the reaction mixture by silica gel column chromatography (eluent; hexane : ethyl acetate = 1 : 1) and recrystallization from hexane / ethyl acetate gave (*R*)-(-)-ethosuximide {36.3 mg, 82%, mp 63-64 °C, $[\alpha]_D^{24}$ -25.2° (*c* 0.68, $CHCl_3$), 88% ee; Lit.,[3] $[\alpha]_D^{24}$ -28.0° (*c* 0.83, $CHCl_3$), 97% ee} as colorless needles, whose spectroscopic data and a chiral HPLC analysis were identical with those of the sample prepared previously.[3]

(*S*)-(+)-2-Methyl-2-(2-oxopropyl)-4-butanolide [(+)-7]

To an ethanol solution (50 mL) of (*S*)-2-methyl-2-[(*E*)-2-nitropropenyl]-4-butanolide [(-)-**2b**] (91% ee) (4.50 g, 24.3 mmol) was added sodium borohydride (1.10 g, 29.2 mmol) at 0 °C, and the mixture was stirred for 15 min. The reaction mixture was quenched with 10% hydrochloric acid (25 mL), stirred for 2.75 h, and concentrated under reduced pressure, then extracted with ethyl acetate (30 mL x 4). The organic layer was washed with brine (20 mL x 4), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent; hexane : ethyl acetate = 4 : 1) to give (+)-**7** (3.20 g, 85%). (+)-**7**: pale yellow oil; $[\alpha]_D^{18}$ +20.9° (*c* 2.06, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.28 (s, 3H), 2.06 (dd of ABd, J_{AB} = 12.6 Hz, J = 7.6 and 3.1 Hz, 1H), 2.16 (s, 3H), 2.40 (t of ABd, J_{AB} = 12.6 Hz, J = 9.1 Hz, 1H), 2.83 (ABd, J_{AB} = 18.4 Hz, 1H), 2.87 (ABd, J_{AB} = 18.4 Hz, 1H), 4.27 (dd of ABd, J_{AB} = 9.1 Hz, J = 9.1 and 7.6 Hz, 1H), 4.33 (dd of ABd, J_{AB} = 9.1 Hz, J = 9.1 and 3.1 Hz, 1H); IR ($CHCl_3$): 3000, 2920, 1765, 1715, 1455, 1400, 1360, 1165, 1100, 1030 cm^{-1}; MS (FAB) *m/z* 157 (M^++H, 100); HRMS (FAB) calcd for $C_8H_{13}O_3$ (M^++H) 157.0865, found: 157.0859.

(*S*)-(+)-2-Carboxymethyl-2-methyl-4-butanolide [(+)-8][3]

A mixture of (+)-**7** (16.0 mg, 0.102 mmol) and 13% sodium hypochlorite solution (2 mL, 3.5 mmol) was stirred at 50 °C for 10 h. The reaction mixture was quenched with 10% hydrochloric acid (10 mL) and stirred for 2 h at rt, and then extracted with ethyl acetate (10 mL x 6). The organic layer was washed with brine (10 mL x 2), dried over anhydrous magnesium sulfate, filtered, and concentrated *in vacuo*. The resultant solid was recrystallized from ethyl acetate to give (+)-**8** {15.0 mg, 97%, mp 107-108 °C, $[\alpha]_D^{21}$ +2.59° (*c* 1.02, $CHCl_3$); Lit.,[3] $[\alpha]_D^{18}$ +2.63° (*c* 1.40, $CHCl_3$)} as colorless crystalline, whose spectroscopic data were identical with those of the sample prepared previously.[3]

(*S*)-(-)-2-Benzylthioethyl-2-methylbutanedioic Acid [(-)-9][3]

Benzyl mercaptan (1.55 mL, 13.25 mmol) was added to a suspension of sodium hydride (60% in mineral oil, 529.9 mg, 13.25 mmol), which was washed with ether (4 mL), in dimethylformamide (DMF) (20 mL) at 0 °C under nitrogen atmosphere. After the evolution of hydrogen gas ceased (*ca.* 15 min), a DMF (5 mL) solution of (+)-**8** (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 (-)-**9** {1.12 g, 90%, mp 54-55 °C; $[\alpha]_D^{19}$ -1.86° (*c* 0.72, $CHCl_3$); Lit.,[3] $[\alpha]_D^{26}$ -1.97° (*c* 0.82, $CHCl_3$)} as colorless crystalline, whose spectroscopic data were identical with those of the sample prepared previously.[3]

(*S*)-(+)-Dimethyl 2-Ethyl-2-methyl-1,4-butanedioate [(+)-10]

To an ether solution (50 mL) of (-)-**9** (4.0 g, 14.2 mmol) was added diazomethane at 0 °C and the resultant mixture was kept on standing for 15 min. Acetic acid was added to the reaction mixture to decompose the excess diazomethane, then the resultant mixture was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent; hexane : ethyl acetate = 4 : 1) to give dimethyl (*S*)-(-)-2-benzylthioethyl-2-methyl-1,4-butanedioate (4.10 g, 93%). dimethyl (*S*)-(-)-2-benzylthioethyl-2-methyl-1,4-butanedioate: pale yellow oil; $[\alpha]_D^{22}$ -4.03° (*c* 0.67, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.22 (s, 3H), 1.78 (dd of ABd, J_{AB} = 13.8 Hz, J = 10.9 and 6.2 Hz, 1H), 1.92 (dd of ABd, J_{AB} = 13.8 Hz, J = 10.9 and 5.8 Hz, 1H), 2.27-2.43 (m, 2H), 2.40 (ABd, J_{AB} = 16.0 Hz, 1H), 2.73 (ABd, J_{AB} = 16.0 Hz, 1H), 3.64 (s, 3H), 3.65 (s, 3H), 3.70 (s, 2H), 7.24-7.32 (m, 5H); IR ($CHCl_3$): 3000, 2950, 1740, 1720, 1490, 1450, 1435, 1355, 1170, 1010 cm^{-1}; MS (FAB) *m/z* 311 (M^++H, 41); HRMS (FAB) calcd for $C_{16}H_{23}O_4S$ (M^++H) 311.1317, found: 311.1333.

To an ethanol solution (20 mL) of dimethyl (*S*)-(-)-2-benzylthioethyl-2-methyl-1,4-butanedioate (500 mg, 1.61 mmol) was added freshly prepared Raney nickel (W-2) (suspension in ethanol, 20 mL), then the suspension was refluxed for 8 h. Raney nickel was filtered on celite and washed with hot methanol, then the combined filtrate was concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (eluent; hexane : ethyl acetate = 5 : 1) to give (+)-**10** (269 mg, 89%). (+)-**10**: pale yellow oil; $[\alpha]_D^{23}$ +6.14° (*c* 0.46, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 0.85 (t, J = 7.5 Hz, 3H), 1.24 (s, 3H), 1.56 (q of ABd, J_{AB} = 14.1 Hz, J = 7.5 Hz, 1H), 1.68 (q of ABd, J_{AB} = 14.1 Hz, J = 7.5 Hz, 1H), 2.40 (ABd, J_{AB} = 15.9 Hz, 1H), 2.79 (ABd, J_{AB} = 15.9 Hz, 1H), 3.66 (s, 3H), 3.70 (s, 3H); IR ($CHCl_3$): 2950, 1730, 1460, 1435, 1380, 1350, 1170, 1140, 1000, 980 cm^{-1}; MS (FAB) *m/z* 189 (M^++H, 17); HRMS (FAB) calcd for $C_9H_{17}O_4$ (M^++H) 189.1127, found: 189.1113.

(*S*)-(+)-2-Ethyl-2-methylsuccinimide [(*S*)-(+)-ethosuximide][3,4d]

The same procedure as a preparation of (*R*)-(-)-ethosuximide using (+)-**10** (800 mg, 4.25 mmol) and urea (2.55 g, 42.5 mmol) gave (*S*)-(+)-2-ethyl-2-methylsuccinimide [(*S*)-(+)-ethosuximide] {580 mg, 96%, 98% ee, mp 64-66 °C, $[\alpha]_D^{22}$ +28.4° (*c* 0.42, $CHCl_3$); Lit.,[3] $[\alpha]_D^{25}$ +28.6° (*c* 0.47, $CHCl_3$)} as colorless needles, whose spectroscopic data and a chiral HPLC analysis were identical with those of the sample prepared previously.[3]

(1'*R*, 2*S*)-(+)-2-Methyl-2-{(1'-phenylethyl)carbamoylmethyl}-4-butanolide [(+)-11]

To a dichloromethane solution (3 mL) of (+)-**8** (22 mg, 0.139 mmol, 97% ee) were added (*R*)-1-phenylethylamine (22 μL, 0.167 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (WSC) (53.0 mg, 0.278 mmol) at rt and the mixture was stirred for 13 h. The reaction mixture was poured into 1% hydrochloric acid and extracted with ethyl acetate (10 mL x 5). The organic layer was washed with brine (10 mL x 2), dried over anhydrous magnesium sulfate, filtered and concentrated *in*

vacuo. The crude product was purified by silica gel preparative thin layer chromatography (eluent; ethyl acetate) to give (+)-**11** (33.1 mg, 91%) as colorless needles. (+)-**11**: mp 146.7-147.9 ℃ (hexane / ethyl acetate); $[\alpha]_D^{22}$ +77.3° (*c* 0.075, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ: 1.32 (s, 3H), 1.47 (d, J = 6.9 Hz, 3H), 2.04 (dd of ABd, J_{AB} = 13.0 Hz, J = 6.6 and 3.8 Hz, 1H), 2.40 (ABd, J_{AB} = 14.3 Hz, 1H), 2.43 (t of ABd, J_{AB} = 13.0 Hz, J = 8.9 Hz, 1H), 2.60 (ABd, J_{AB} = 14.3 Hz, 1H), 4.18-4.29 (m, 2H), 5.07 (quintet, J = 6.9 Hz, 1H), 6.15 (br d, J = 6.9 Hz, 1H), 7.23-7.36 (m, 5H); IR ($CHCl_3$): 3032, 2361, 2341, 1223, 1211, 1202 cm-1; MS (FAB) *m/z* 262 (M^++H, 100); HRMS (FAB) calcd for $C_{15}H_{20}NO_3$ (M^++H) 262.1443, found: 262.1445.

An X-Ray Crystallographic Analysis of (+)-11

The orthorhombic crystal was observed with a couple of two different conformers: $C_{15}H_{19}NO_3$, M = 261.32, orthorhombic, space group $P2_12_12_1$ (#19), a = 16.822(2) Å, b = 17.778(2) Å, c = 9.967(3) Å, V = 2980.8(9) Å^3, Z = 8, D_{calc} = 1.165 g/cm^3, μ = 6.58 cm^{-1}, T = 296 K, 2546 measured reflections, 1587 reflections with $I > 3.00\sigma(I)$ used in refinement, R = 0.037, R_w = 0.051. The data were collected using a Rigaku AFC7R diffractometer with graphite-monochromated Cu-Kα radiation (λ = 1.54178 Å) by the ω-2θ scan technique in the range 56.43 < 2θ < 59.57°. The structure was solved by direct methods (MITHRIL84) and expanded using Fourier techniques. The non-hydrogen atoms were refined anisotropically. The hydrogen atoms were included but not refined.

Anticonvulsant Activity of (+)- and (-)-Ethosuximides to Mice Treated with Metrazol (Table 1)

Male 5 weeks old ddY mice (SLC, Japan) were treated intravenously with aqueous solution of one of ethosuximide enantiomers [(*S*): >99% ee, (*R*): 97% ee] or saline (0.1 mL / 10 g body weight) and were challenged by intraperitoneal injection of 150 mg/kg metrazol 5 min later. Occurrence of clonic seizure, tonic extension of hind limbs and death were observed for 10 min thereafter.

REFERENCES AND NOTE

1. For asymmetric nitroolefination see: a) K. Nishide, R. Kurosaki, K. Hosomi, H. Imazato, T. Inoue, M. Node, T. Ohmori, and K. Fuji, *Tetrahedron*, 1995, **51**, 10857. b) M. Node, R. Kurosaki, K. Hosomi, T. Inoue, K. Nishide, T. Ohmori, and K. Fuji, *Tetrahedron Lett.*, 1995, **36**, 99. c) K. Fuji, T. Kawabata, T. Ohmori, and M. Node, *Synlett*, 1995, 367. d) K. Fuji, T. Kawabata, Y. Naniwa, T. Ohmori, and M. Node, *Chem. Pharm. Bull.*, 1994, **42**, 999. e) K. Fuji and M. Node, *Synlett*, 1991, 603. f) M. Node and K. Fuji, *J. Syn. Org. Chem. Jpn.*, 1990, **48**, 389. g) K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, T. Taga, K. Machida, and G. Snatzke, *J. Am. Chem. Soc.*, 1989, **111**, 7921. h) M. Node, H. Nagasawa, Y. Naniwa, and K. Fuji, *Synthesis*, 1987, 729. i) K. Fuji, M. Node, H. Nagasawa, Y. Naniwa, and S. Terada, *J. Am. Chem. Soc.*, 1986, **108**, 3855.
2. For application of asymmetric nitroolefination see: a) M. Node, H. Nagasawa, and K. Fuji, *J. Org. Chem.*, 1990, **55**, 517. b) M. Node, H. Nagasawa, and K. Fuji, *J. Am. Chem. Soc.*, 1987, **109**, 7901. c) M. Node, X.-J. Hao, K. Nishide, and K. Fuji, *Chem. Pharm. Bull.*, 1996, **44**, 715. d) M. Node, X.-J. Hao, and K. Fuji, *Chem. Lett.*, 1991, 57. e) M. Node, A. Itoh, Y. Masaki, and K. Fuji, *Heterocycles*, 1991, **32**, 1705. f) X.-J. Hao, M. Node, and K. Fuji, *J. Chem. Soc., Perkin Trans. I*, 1992, 1505. g) K. Fuji, S.-Z. Zheng, M. Node, and X.-J. Hao, *Chem. Pharm. Bull.*, 1991, **39**, 202. h) M. Node, X.-J. Hao, H. Nagasawa, and K. Fuji, *Tetrahedron Lett.*, 1989, **30**,

4141.
3. K. Nishide, T. Katoh, H. Imazato, and M. Node, *Heterocycles*, 1998, **47**, 839.
4. For synthesis of (±)-ethosuximide see: a) P. A. S. Smith and J. P. Horwitz, *J. Am. Chem. Soc.*, 1949, **71**, 3418. b) S. S. G. Sircar, *J. Chem. Soc.*, 1927, 1252. c) H. Ishibashi, T. Nakaharu, M. Nishimura, A. Nishikawa, C. Kameoka, and M. Ikeda, *Tetrahedron*, 1995, **51**, 2929.
For synthesis of (+)- and (-)-ethosuximides: d) J. Knabe and W. Koch, *Arch. Pharm.*, 1972, **305**, 757. e) J. Knabe and J. Plisch, *Tetrahedron Lett.*, 1973, 745.
5. a) L. Sorel, *Acta Neurol. Psychiat. Belg.*, 1960, **60**, 551. b) T. Hirai, N. Ando, T. Naoi, R. Inoue, and H. Watanabe, *Seishin Igaku*, 1965, **7**, 142.
6. It is considered that the enhancement of optical purity (91 → 98% ee) occurred when acids (**8**, **9**) and (*S*)-ethosuximide crystallized.
7. T. R. Kelly, H. M. Dali, and W.-G. Tsang, *Tetrahedron Lett.*, 1977, 3859.
8. J. F. Reinhard and J. F. Reinhard, Jr., 'Anticonvulsants: Experimental Evaluation of Anticonvulsants' ed. by J. Aavida, Academic Press, Inc., New York, 1977, pp. 55-111.

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