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A NEW NONENZYMATIC CHIRAL INDUCTION INTO PROCHIRAL MESO COMPOUNDS

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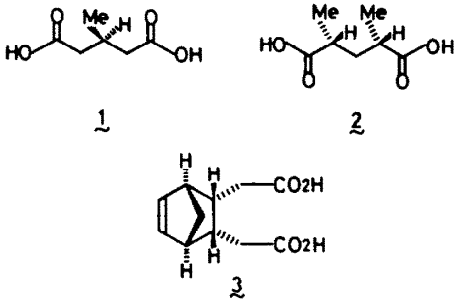
Abstract—The highly selective asymmetric induction into prochiral meso compounds has been developed by utilizing a functional heterocycle, 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione.

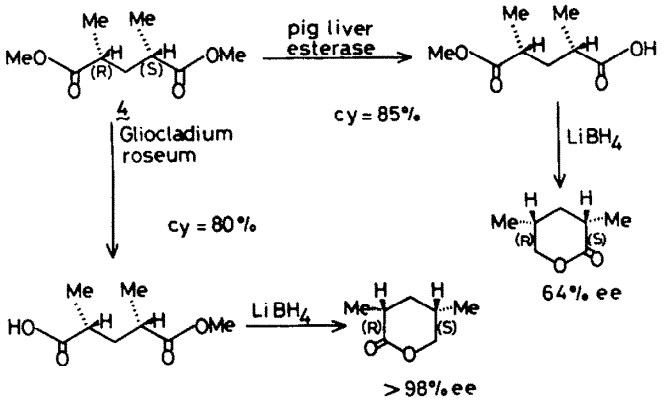
The chemical asymmetric syntheses have extensively been progressing.[1] Among these, the methodology utilizing the molecular regulation by the metal chelation has been most popular. Recently, however, the strategies based on the symmetry element of organic molecules are being noticed.[2] We are also developing a novel procedure.



First, we reported a novel and useful nonenzymatic procedure for a highly selective asymmetric induction to a prochiral center in a symmetrical molecule, 3-methylglutaric acid (**1**),[3] and proposed a new concept that the introduction of the same chiral ligands, into a symmetrical molecule having a prochiral center can change its original symmetrical environment into an unsymmetrical environment.[3] This novel concept should be widely applicable to the various symmetrical prochiral compounds. Thus, we succeeded in an extremely regioselective high-differentiation between two identical groups in *meso*-2,4-dimethylglutaric acid (**2**) and communicated it very recently.[4]

We wish to report herein the full details of the nonenzymatic chiral induction into two prochiral meso compounds, *meso*-2,4-dimethylglutaric acid (**2**) and *meso-cis*-5-norbornene-endo-2,3-diacetic acid (**3**).

The highly regio-selective transformation of dimethyl *meso*-2,4-dimethylglutarate (**4**) was only performed by a special microorganism, *Gliocraudium roseum* (Scheme 1); it was reported by Sih's group.[5] Any chemical method, however, has never been presented.



Scheme 1

meso-2,4-Dimethylglutaric anhydride **6**, obtained from a mixture of *meso*- and *dl*-2,4-dimethylglutaric acid (**2** and **5**) by the known procedure,[6] was treated with 2 molar equiv of 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione [4(*R*)-MCTT] in the presence of DCC in pyridine–CH_2Cl_2 (5:1) to give diamide **7** in 64.1% yield (Scheme 2). Diamide **7** on aminolysis with piperidine in CH_2Cl_2 at $-20°$ afforded a solid mixture (66.3% yield), which was found to consist of **8** and **9** in a 97.5:2.5 ratio by HPLC analysis. Recrystallization of the mixture from CH_2Cl_2–petroleum ether only once gave the major product **8** (overall 58.4% yield from **7**) as pure yellow plates (m.p. 111–112°) (Scheme 2). The structure and absolute stereochemistry were established by X-ray analysis. A perspective view of the crystallographic structure **8** is shown in Fig. 1.[7] As the result, it was clarified that the piperidine nucleophile predominantly attacked the carbonyl C atom attached to the (*S*)-methyne C atom.

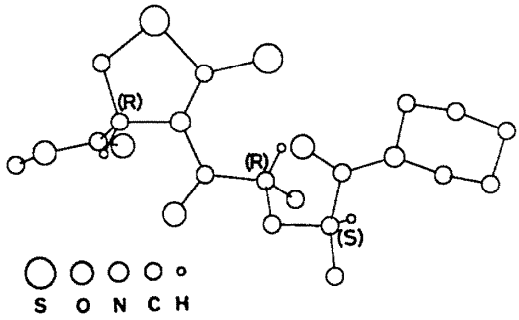


Fig. 1. Perspective view of the crystallographic structure of compound **8**.

Speculation based on the X-ray crystallographic structure of the major product **8** led to a hypothetical transition state (see Fig. 2), in which approach of the piperidine molecule should be regulated because of hindered left-hand CO group at both α- and β-faces and of hindered α-face of the right-hand CO group.

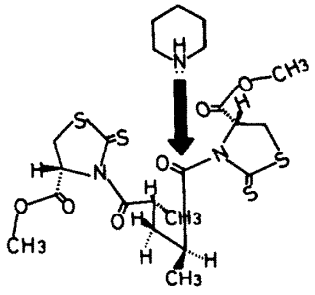
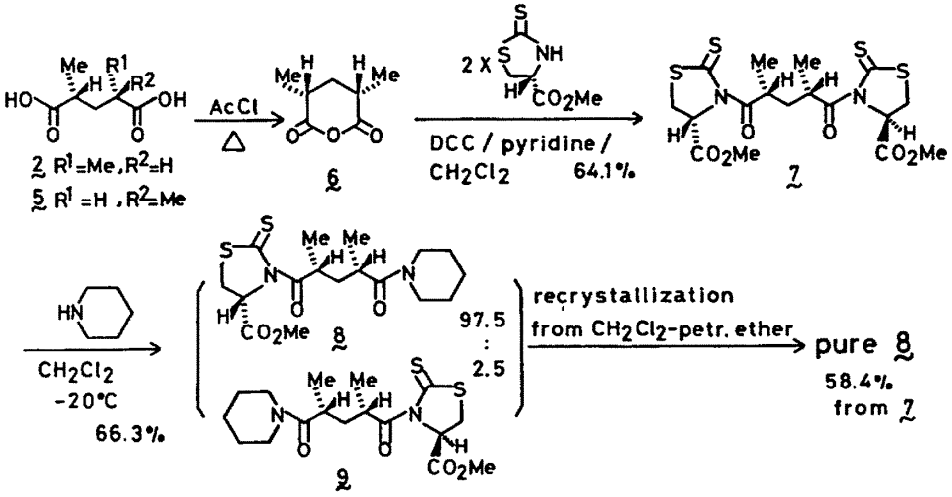


Fig. 2.

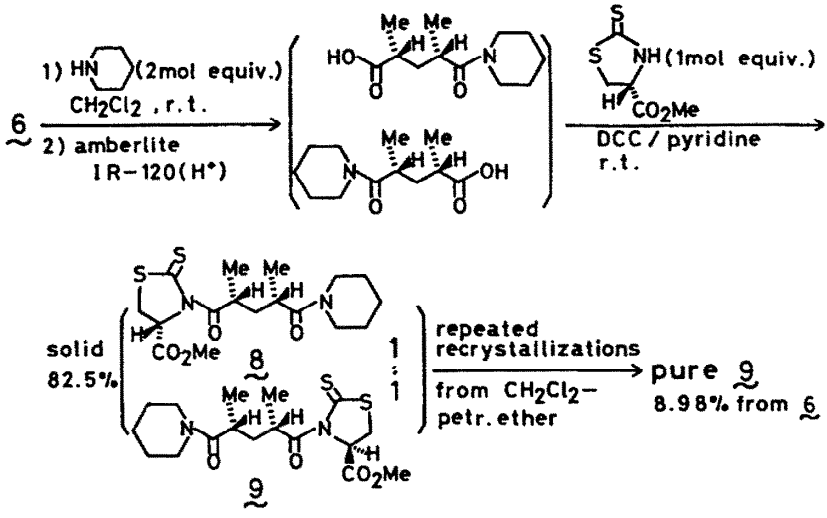
In order to get the minor product **9** in sufficient quantity, the synthetic procedure illustrated in Scheme 3 was tried. The anhydride **6** was treated with 2 molar equiv of piperidine in CH_2Cl_2 at room temperature then with Amberlite IR-120(H^+) to yield a racemic monoamide. The usual treatment of this racemate with 4(*R*)-MCTT (1 molar eqiv) gave a solid mixture of diastereomers **8** and **9** in a ratio 1:1. Repeated recrystallization of the resulting mixture afforded pure crystals **9** (m.p. 135–135.5°). Its absolute structure was determined by the X-ray analysis: a perspective view of the crystallographic structure of **9** is illustrated in Fig. 3.[7] The stereochemistry of **9** was also confirmed by its conversion into the enantiomer (**11**) of compound **10a** derived from **8** (Scheme 4 and Table 1).

Subsequently, the major product **8** was subjected to "the monitored reaction"[8] with some nucleophile to afford enantiomeric pure acyclic products **10a–d** in high yields (Scheme 4 and Table 1).

It was confirmed by the ^{1}H-NMR (100 MHz) analysis of products **10a–d** that no epimerization occurred at all during the conversion from **7** into **10**. We prepared a pure methyl ester **12** and the epimeric mixture (**12** and **13**) from **7** under the different methanolytic conditions which are shown in Scheme 5. Epimerization of the asymmetric methyne C atom of the ester site was confirmed by the incorporation of D atom giving a mixture of mono deuterio com-



Scheme 2



Scheme 3

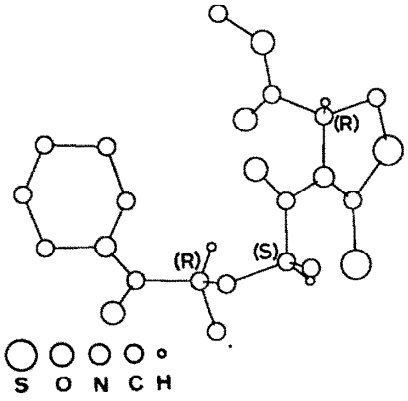
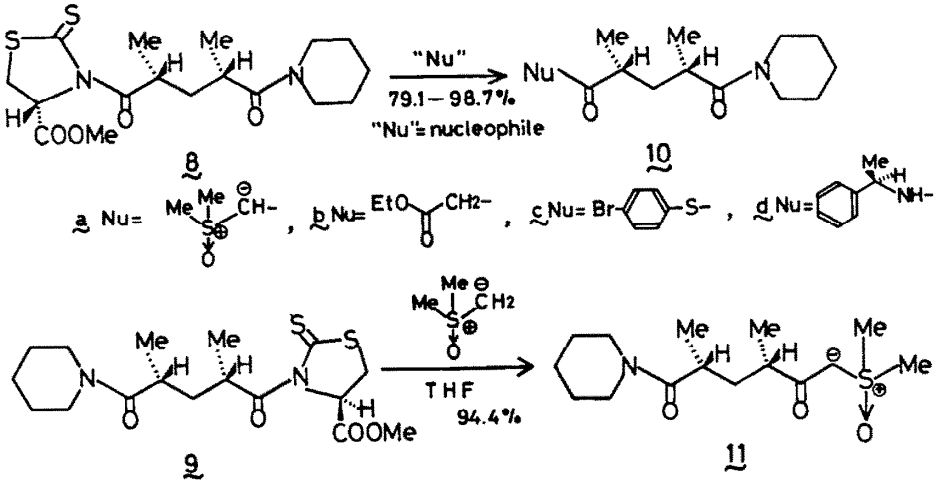


Fig. 3. Perspective view of the crystallographic structure of compound **9**.

pounds **14** and **15**. On the ^{1}H-NMR spectrum of the epimeric mixture of **12** and **13** or of **14** and **15**, signals (δ 1.07 and 1.10) assignable to the Me protons a C-4 were observed as two set of doublets (each $J = 5$ Hz). On the other hand, the ^{1}H-NMR spectra of **10** and **12** synthesized under mild basic conditions showed a sharp doublet signal due to the Me protons at C-4.

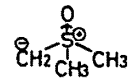
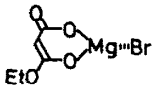
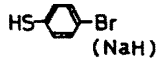
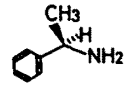
Finally, we attempted the similar chiral induction utilizing 4(*R*)-MCTT into a cyclic meso compound, *meso-cis*-5-norbornene-endo-2,3-diacetic acid (**3**). The material was derived from a comercially avaialbe diacid **16** *via* 4 steps of reactions (Scheme 6).

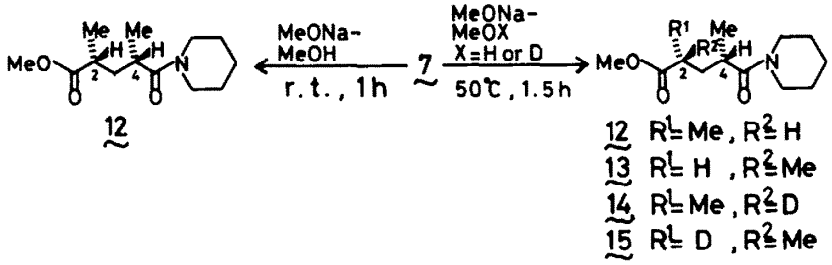
Diamide **19** was prepared by the usual treatment of diacid **3** and 2 molar equiv of 4(*R*)-MCTT with DCC in pyridine. The selective aminolysis of diamide **19** with 1 molar equiv of piperidine was successfully carried out in CH_2Cl_2 at $-78°$ to give a solid mixture (66.3%), which was found to consist of **20** and **21** in



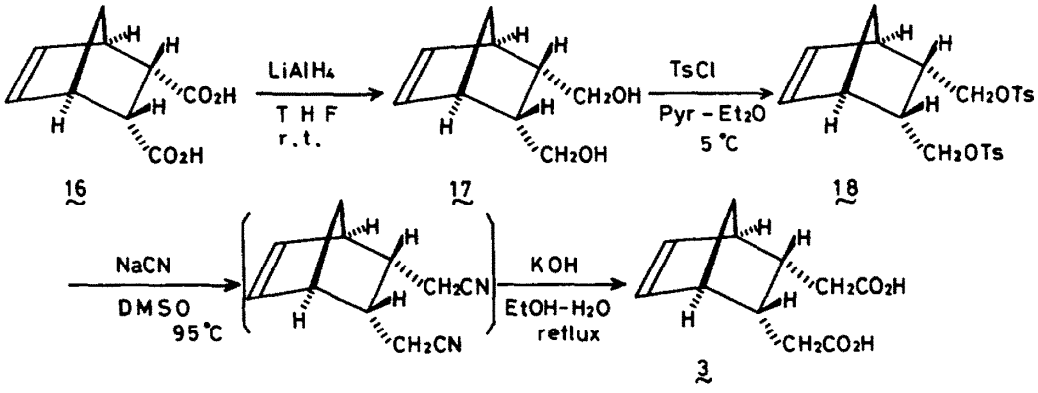
Scheme 4

Table 1. Reactions of **8** and **9** with some nucleophiles

nucleophile	product	mp, °C	$[\alpha]_D^{25}$ deg ($CHCl_3$)	yield %
	10a	110-111	-19.08 (c 1.09)	94.0
〃	11	110-111	+19.11 (c 1.10)	94.4
	10b	oil	+5.90 (c 2.03)	79.1
 (NaH)	10c	oil	-9.95 (c 1.19)	98.7
	10d	oil	+57.66 (c 1.07)	93.3



Scheme 5

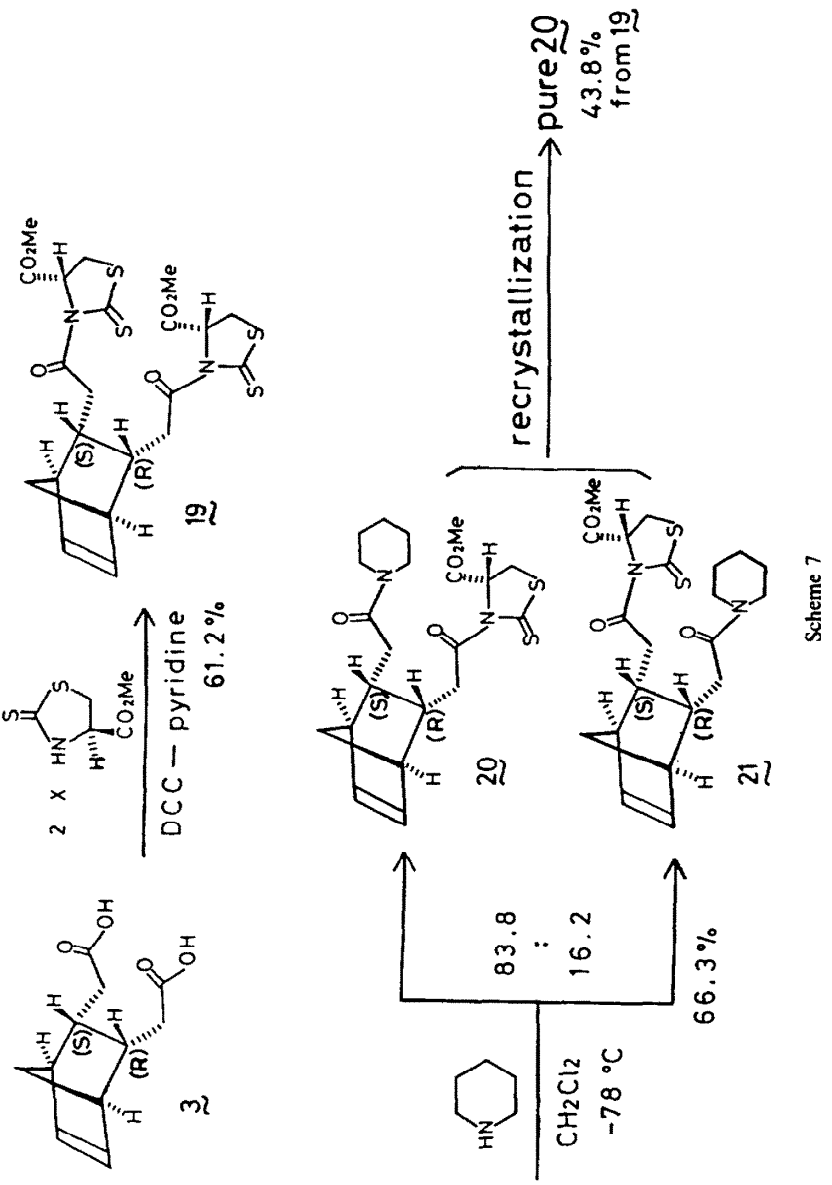


Scheme 6

a 83.3 and 16.2 ratio. The mixture was repeatedly recrystallized from n-hexane–CH_2Cl_2 to afford the major product **20** (overall 43.8% yield from **19**) as yellow needless (m.p. 130–130.5°) (Scheme 7). The structure and absolute stereochemisty were determined by X-ray analysis. A perspective view of the crystallographic structure of **20** is shown in Fig. 4.

From the consideration based on the X-ray analysis of the major product **20**, a plausible transition state illustrated in Fig. 5 may be speculated.

Compounds **10a–d** and **11** should be useful as "bifunctional, optically active synthon" for total synthesis of the Prelog–Djerassi lactonic acid (**22**)[6b,9] methynolide (**23**),[10] 6-deoxyerythronolide B (**24**),[11]


3
2 X
DCC — pyridine
61.2 %
19
CH2Cl2
-78 °C
83.8
:
16.2
66.3 %
20
21
recrystallization
pure 20
43.8 %
from 19

Scheme 7

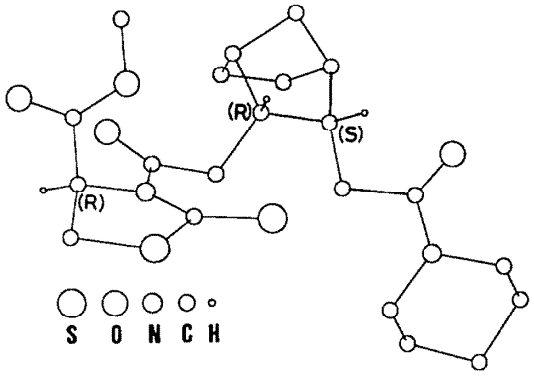


Fig. 4. Perspective view of the crystallographic structure of compound **20**.

EXPERIMENTAL

M.ps were determined with a Yanagimoto micro-apparatus. IR spectra were recorded on a JASCO A-202 spectrophotometer and optical rotations were measured on a JASCO DIP-181 polarimeter. Mass spectra were recorded on JEOL JMS-DX300 and Hitachi M-80 mass spectrometers. ^{1}H-NMR spectra were determined in $CDCl_3$ with a JEOL JMN-FX100 (100 MHz) spectrometer; signals are given in ppm from $SiMe_4$ as internal standard. High-pressure liquid chromatography was performed by JASCO Tri Rotar (UV-100) equipped with JASCO DP-L220 LC data processor. Extracts were dried over anhydrous Na_2SO_4. Merck silica gel 60H was used for flash column chromatography.[16]

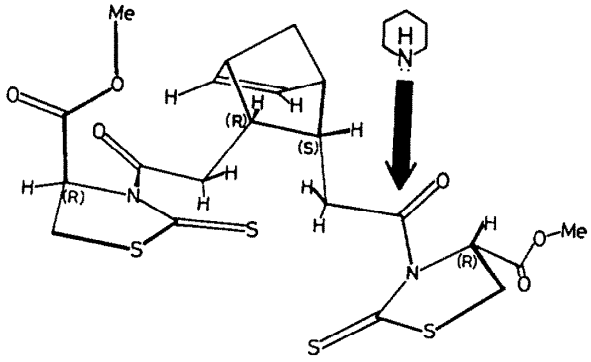
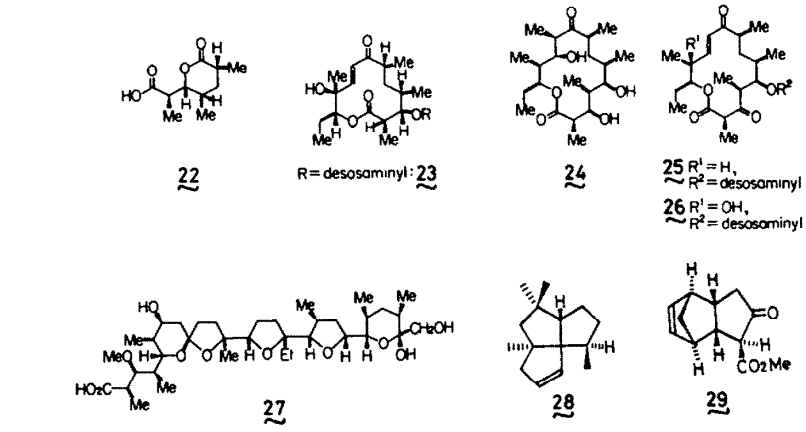


Fig. 5.

narbomycin (**25**),[12] pikromycin (**26**),[13] and monensin (**27**).[14] Compound **20** may be applied for total synthesis of (-)-silphinene (**28**)[15] *via* a tricyclic intermediate **29**.

Preparation of diamide **7**

A soln of *meso-cis*- **6**, (5.560 g, 39.15 mmol) in CH_2Cl_2 (20 ml) was added to a soln of 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione (13.860 g, 78.30 mmol)



Thus, we provided a novel and valuable procedure for the highly selective asymmetric induction into prochiral meso compounds. The further application of this procedure to total synthesis of optically active, pure natural products is now in progress.

and DCC (16.129 g, 78.30 mmol) in pyridine (100 ml). The mixture was stirred at room temp under N_2 for 5 days and a large amount of toluene was added. The solvent of the mixture was evaporated off *in vacuo* to give an oily residue, which was treated with AcOEt. The ppt (DCC urea) from the AcOEt soln was filtered off and the filtrate was con-

densed *in vacuo* to give an oily residue, which was purified by the flash chromatography on a silica gel column with benzene–AcOEt (7:2) to afford **7** (12 g, 64.1% yield) as a yellow oil. $[\alpha]_D^{20}$-169.23° (c = 1.05, $CHCl_3$); ^{1}H-NMR δ 1.20 (3H, d, J = 7.1 Hz), 1.29 (3H, d, J = 6.8 Hz), 1.44–1.80 (1H, m), 2.16–2.56 (1H, m), 3.20–3.90 (4H, m), 3.81 (3H, s), 3.83 (3H, s), 4.28–4.84 (2H, m), and 5.54–5.70 (2H, m); IR ($CHCl_3$) 1757 and 1700 cm^{-1}; (Found: M^+, 478.0388. $C_{17}H_{22}O_6N_2S_4$ Requires: M, 478.0361).

Aminolysis of diamide **7**

A soln (3.61 ml) of piperidne (1 g) in CH_2Cl_2 (10 ml) was dropwise added to a soln of **7** (1.817 g, 3.80 mmol) in CH_2Cl_2 (100 ml) at − 20° under N_2 with stirring. After being stirred at − 20° overnight, the mixture was evaporated *in vacuo* to give a yellow oily residue, which was checked by HPLC using the following analytical conditions: column, JASCO PACK SS-05-250; solvent system, benzene–AcOEt (4:1); pressure, 150 kg/cm^2. Retention times: 14.39 min and 11.38 min for **8** and **9**, respectively. Then, the residue was chromatographed by the flash technique on a short silica gel column with benzene and then with benzene–AcOEt (9:1) to afford a mixture (0.973 g, 66.3% yield) of **8** and **9** as yellow crystals. Recrystallization of the mixture from CH_2Cl_2–petroleum ether only once gave a sole pure compound **8** (0.858 g, 58.4% yield) as yellow plates. m.p. 111–112°; $[\alpha]_D^{20}$-113.79° (c = 1.10, $CHCl_3$); ^{1}H-NMR δ 1.07 (3H, d, J = 6.6 Hz), 1.27 (EH, d, J = 6.8 Hz), 1.30–1.80 (7H, m), 2.00–2.36 (1H, m), 2.50–2.96 (1H, m), 3.20–3.80 (4H, m), 3.36 (1H, dd, J = 11.7 and 2.2 Hz), 3.74 (1H, dd, J = 11.7 and 8.3 Hz), 3.81 (3H, s), 4.24–4.60 (1H, m), and 5.69 (1H, dd, J = 8.3 and 2.2 Hz); IR ($CHCl_3$) 1754, 1702, and 1618 cm^{-1}; (Found: C, 52.38; H, 6.93; N, 7.24; M^+ 386. $C_{17}H_{26}O_4N_2S_2$ Requires: C, 52.83; H, 6.78; N, 7.25; M 386).

Preparation of diamide **9**

A soln of piperidine (3.341 g, 39.238 mmol) in CH_2Cl_2 (30 ml) was added to a soln of *meso-cis-* **6** (2.786 g, 19.619 mmol) in CH_2Cl_2 (30 ml). The mixture was stirred at room temp for 1 hr and the solvent was evaporated *in vacuo* to give an oily residue, which was dissolved in a minimum amount of water. After being passed through a column prepared from Amberlite IR-120 (H^+ type) and water, the water soln was perfectly evaporated *in vacuo* to give a viscid oily residue. To this residue was added a soln of 4(*R*)-MCTT (3.472 g, 19.619 mmol) and DCC (5.253 g, 25.505 mmol) in pyridine (100 ml). The mixture was stirred at room temp under N_2 for 2 days. Evaporation of the solvent *in vacuo* gave an oily residue, to which a large amount of EtOAc was added. The ppt (DCC urea) was filtered off and the filtrate was condensed *in vacuo* to give a yellow oil, which was subjected to the flash chromatography on a short silica gel column with benzene-AcOEt (4:1) to give the mixture (6.250 g, 82.5% yield) of the diastereomers **8** and **9** as yellow crystals. This crystalline mixture was repeatedly recrystallized from CH_2Cl_2–petroleum ether to afford pure **9** (681 mg, overall 8.98% yield from **6**) as yellow needles. m.p. 135–135.5°; $[\alpha]_D^{20}$-46.35° (c = 1.62, $CHCl_3$); ^{1}H-NMR δ 1.12 (3H, d, J = 6.8 Hz), 1.20 (3H, d, J = 7.1 Hz), 1.30–1.80 (7H, m), 2.00–2.30 (1H, m), 2.52–2.94 (1H, m), 3.20–3.80 (4H, m), 3.36 (1H, dd, J = 11.7 and 2.9 Hz), 3.70 (1H, dd, J = 11.7 and 8.5 Hz), 3.82 (3H, s), 4.60–5.00 (1H, m), and 5.68 (1H, dd, J = 8.5 and 2.9 Hz); IR ($CHCl_3$) 1759, 1701 and 1618 cm^{-1}; (Found: C, 52.95; H, 6.93; N, 7.22; M^+ 3.86. $C_{17}H_{26}O_4N_2S_2$ Requires: C, 52.83; H, 6.78; N, 7.25; M 386).

Treatment of **8** *with dimethyloxosulfonium methylide*

A mixture of trimethyloxosulfonium chloride (578 mg, 4.5 mmol)[17] and NaH (144 mg, 3.6 mmol) in THF (5 ml) was refluxed under N_2 for 2 hr. The mixture was cooled to room temp and a soln of **8** (386 mg, 1 mmol) in THF (5 ml) was added. After being stirred for 15 min, the solvent of the mixture was evaporated *in vacuo* to give a residue, which was chromatographed by the flash technique on a short silica gel column with benzene–AcOEt (1:1) and with $CHCl_3$–MeOH (10:1) to afford **10a** (285 mg, 94.0% yield) as colorless needles from CH_2Cl_2–*n*-hexane. m.p. 110–111°; $[\alpha]_D^{25}$-19.08° (c = 1.09, $CHCl_3$), ^{1}H-NMR δ 1.02, 1.08, 1.09, 1.14 (6H, two doublets), 1.20–1.70 (7H, m), 1.80–3.00 (3H, m), 3.40 (6H, s), 3.20–3.70 (4H, m), and 4.48 (1H, s); IR ($CHCl_3$) 1616; (Found: C, 59.64; H, 9.16; N, 4.57; M^+ 302. $C_{15}H_{27}O_3NS$ Requires: C, 59.77; H, 9.05; N, 4.65; M 302).

Dimethyloxosulfonium ylide **11**

The compound **11** was prepared by the similar treatment of amide **9** with dimethyloxo-sulfonium methylide as in the case of **10a**; 94.4% yield; colorless needles from CH_2Cl_2 –*n*–hexane: m.p. 110–111°; $[\alpha]_D^{25}$ + 19.11° (c = 1.10 $CHCl_3$); ^{1}H-NMR δ 1.02, 1.08, 1.09, 1.14 (6H, two doublets), 1.20–1.70 (7H, m), 1.80–3.00 (3H, m), 3.40 (6H, s), 3.20–3.70 (4H, m), and 4.48 (1H, s); IR ($CHCl_3$) 1616 cm^{-1}; (Found: C, 59.57; H, 9.11; N, 4.66; M^+ 302. $C_{15}H_{27}O_3NS$ Requires: C, 59.77; H, 9.05; N, 4.65; M 302).

Preparation of β-keto ester **10b**

A soln of ethyl hydrogen malonate (0.282 ml, 2.5 mmol) in THF (2 ml) was dropwise added to a THF soln (5.1 ml) of *iso*-PrMgBr (5.1 mmol) at room temp with stirring.[18] The mixture was stirred at room temp for 30 min and then a soln of **8** (386 mg, 1 mmol) in THF (5 ml) was added at 0°. After being stirred at room temp overnight, the mixture was poured into cold 10% HCl aq and extracted with $CHCl_3$. The extract was washed with brine, dried, and evaporated *in vacuo* to give an oily residue, which was purified by the flash chromatography on a short silica gel column with benzene and with benzene–AcOEt (9:1) to afford **10b** (235 mg, 79.1% yield) as a colorless oil. $[\alpha]_D^{25}$ + 5.90° (c = 2.03, $CHCl_3$); ^{1}H-NMR δ 1.11 (6H, d, J = 7 Hz), 1.27 (3H, t, J = 7.1 Hz), 1.20–1.80 (7H, m), 2.00–2.36 (1H, m), 2.50–3.00 (2H, m), 3.20–3.70 (4H, m), 3.56 (2H, s like), and 4.19 (2H, q, J = 7.1 Hz); IR ($CHCl_3$) 1740, 1714, and 1616 cm^{-1}; (Found: C, 64, 62; H, 9.47; N, 5.18; M^+ 297. $C_{16}H_{27}O_4N$ Requires: C, 64.62; H, 9.15; N, 4.71; M 297).

Preparation of thiol ester **10c**

60% NaH (mineral oil suspension) (80 mg, 2 mmole) was added to a soln of *p*-bromobenzenethiol (378 mg, 2 mmol) in THF (3 ml). After a soln of **8** (386 mg, 1 mmol) in THF (4 ml) was added, the mixture was stirred at room temp under N_2 for 5 min. The reaction was quenched by addition of cold AcOH (3 ml) and the mixture was treated as usual to give **10c** (393 mg, 98.7% yield) as a colorless oil. $[\alpha]_D^{25}$ − 9.95° (c = 1.19, $CHCl_3$); ^{1}H-NMR δ 1.11, 1.18, 1.20, 1.27 (6H, two doublets), 1.04–1.80 (7H, m), 1.96–2.36 (1H, m), 2.56–3.06 (2H, m), 3.10–3.80 (4H, m) and 7.00–7.60 (4H, m); IR ($CHCl_3$) 1701 and 1618 cm^{-1}; (Found: C, 54.09; H, 6.23; N, 3.50; M^+ 399. $C_{18}H_{24}NSBr$ Requires: C, 54.27; H, 6.07; N, 3.52; M 399).

Treatment of **8** *with* (R)-α-*methylbenzylamine*

A soln of (*R*)-α-methylbenzylamine (145 mg, 1.2 mmol) in CH_2Cl_2 (5 ml) was added to a soln of **8** (386 mg, 1 mmol) in CH_2Cl_2 (5 ml). The mixture was stirred at room temp for 30 min and the solvent was evaporated *in vacuo* to give an oily residue, which was subjected to the usual flash column chromatography to afford **10d** (308 mg, 93.3% yield) as a colorless oil. $[\alpha]_D^{25}$ − 57.66° (c = 1.07, $CHCl_3$); ^{1}H-NMR *d* 1.01, 1.08, 1.14 (6H, two doublets), 1.20–1.76 (7H, m), 1.44 (3H, d, J = 6.8 Hz), 1.80–2.90 (3H, m), 3.00–3.70 (4H, m), 4.90–5.24 (1H, m), 6.70–6.96 (1H, br d), and 7.00–7.40 (5H, m); IR ($CHCl_3$) 3450, 3334, 1666 and 1616 cm^{-1}; (Found: M^+, 330.2303. $C_{20}H_{30}N_2O_2$ Requires: M, 330.2303).

Preparation of methyl ester **12**

Na (300 mg) was added to dry MeOH (5 ml) over 10 min with stirring. The mixture was further stirred until the

metallic Na was perfectly dissolved in MeOH and cooled to the room temp. Then a soln of **7** (386 mg, 1 mmol) in dry MeOH (4 ml) was dropwise added. After being stirred at room temp for 1 hr under N_2, the reaction was quenched with cold 10% HCl aq. The mixture was condensed *in vacuo* had extracted with benzene. The benzene extract was washed with brine, dried, and evaporated *in vacuo* to give an oily residue, which was purified by the usual flash column chromatography to afford **12** (183 mg, 75.9% yield) as a colorless oil. $[\alpha]_D^{25}$ - + 2.45°(c = 3.26, $CHCl_3$); ^{1}H-NMR δ 1.10 (3H, d, J = 5 Hz, CH–CH–CON), 1.17 (3H, d, J = 5 Hz, CH_3–CH–COOMe), 1.20–1.80 (7H, m), 1.90–2.24 (1H, m), 2.36–2.96 (2H, m), 3.20–3.80 (4H, m), and 3.67 (3H, s); IR ($CHCl_3$) 1731 and 1622 cm^{-1}; (Found: M^+ 241.1679. $C_{13}H_{23}NO_3$ Requires: M, 241.1678).

Preparation of the epimeric mixture: **12** *and* **13**

Na (350 mg) was added to dry MeOH (3 ml) over 10 min with stirring under N_2. After the metallic Na was perfectly dissolved and the mixture was cooled to the room temp a soln of **7** (400 mg, 1.036 mmol) in dry MeOH (4 ml) was added. The mixture was stirred at 50° for 1.5 hr under N_2 and treated as usual to give the mixture (92 mg, 36.8% yield) of **12** and **13** as a colorless oil.

^{1}H-NMR analysis: Peaks of two kinds of secondary Me protons of the epimeric mixture (**12** and **13**)—δ 1.04, 1.07, 1.09 (shoulder), 1.12, 1.14, and 1.19. Peaks of two kinds of secondary Me protons of the pure compound (**12**)—δ 1.07, 1.12, 1.14, and 1.19.

Thus the peaks at δ 1.04 and 1.09 in the case of the epimeric mixture should be assignable to the secondary Me protons of [HC(4)-CH_3] of the epimer **13**.

Preparation of the epimeric mixture: **14** *and* **15**

A soln of **7** (400 mg, 1.036 mmol) in MeOD (Merck) (4 ml) was added at room temp to a soln made by dissolving Na (350 mg) in MeOD (3 ml) completely. After being stirred at 50° for 1.5 hr under N_2, the mixture was treated as usual to afford the mixture (93.5 mg, 37.2% yield) of **14** and **15** as a colorless oil.

^{1}H-NMR analysis: Peaks of two kinds of secondary Me protons of the epimeric mixture (**14** and **15**)—δ 1.04, 1.07, 1.09 (shoulder), 1.12, and 1.17.

Thus, the peaks at δ 1.04 and 1.09 should be assignable to the secondary Me protons [HC(4)–CH_3] of the epimer **15** and the singlet peak at δ 1.17 should be assignable to the –DC(2)–CH_3 protons of both **14** and **15**.

Mass spectral analysis: Ratios of the peak-height on the mass spectrum: (1) for the mixture of **14** and **15**—m/z 241/m/z 242 = 6.31/100; m/z 242/m/z 243 = 100/23.52.

(2) for the compound **12**—m/z 241/m/z 242 = 100/24.71.

As the result, incorporation of one deuterium atom into molecule **12** was proved.

Reduction of meso-cis-5-*norbornene-endo*-2,3-*dicarboxylic acid* (**16**) *with* $LiAlH_4$

A soln of **16** (20.505 g, 0.1127 mol) in THF (300 ml) was slowly added to a soln of $LiAlH_4$ (8.01 g, 0.2108 mol) in THF (300 ml) under ice-cooling with stirring. The mixture was stirred at room temp overnight and the reaction was quenched with cold water (35 ml) and cold aq 15% NaOH soln (8 ml). The ppt was filtered off and filtrate was concentrated to *ca* 100 ml, to which was added *ca* 100 ml water. The aqueous soln was extracted with Et_2O. The extract was washed with brine, dried, and evaporated *in vacuo* to give crude crystals, which were recrystallized from MeOH–benzene to afford **17** (14.643 g, 84.4% yield) as colorless crystals. m.p. 68.0–68.5°; ^{1}H-NMR δ 1.30–1.50 (2H, m), 2.40–2.60 (2H, m), 2.70–2.90 (2H, m), 3.20–3.70 (4H, m), 4.60 (2H, br s), and 6.03 (2H, t, J = 2 Hz); IR ($CHCl_3$) 3200–3600 cm^{-1}; (Found: M^+ 154.1008 $C_9H_{14}O_2$ Requires: M, 154.0994).

Preparation of p-*toluenesulfonate* **18**

A soln of *p*-tuluenesulfonyl chloreide (37.106 g, 0.1953 mol) in Et_2O (300 ml) was added to a soln of **17** (12.03 g, 0.0781 mol) in pyridine (70 ml) under ice-cooling with stirring. After being stood in a refrigerator for 3 days, the mixture was poured into cold water, and extracted with benzene. The extract was washed with aq 3N-HCl and with brine, dried, and evaporated *in vacuo* to give a solid, which was recrystallized from MeOH—Et_2O to afford **18** (32.082 g, 88.9% yield) as colorless crystals. m.p. 87.5–88°; ^{1}H-NMR δ 1.20–1.60 (2H, m), 2.20–2.70 (2H, m), 2.46 (6H, s), 2.80–3.00 (2H, m), 3.40–3.90 (4H, m), 5.90 (2H, t, J = 2 Hz), and 7.30–7.80 (8H, m); IR ($CHCl_3$) 1600, 1361, and 1173 cm^{-1}; (Found: M^+, 462. $C_{23}H_{26}O_6S_2$ Requires: M, 462).

Conversion of di-tosylate **18** *to dicarboxylic acid* **3**

95% NaCN (3.721 g, 0.0721 mol) was added to a soln of **18** (11.11 g, 0.024 mol) in DMSO (40 ml). The mixture was heated at 95° under N_2 with stirring for 5 hr and poured into cold water. The mixture was extracted with CH_2Cl_2 and the extract was treated as usual to give an oil, which was dissolved in EtOH (50 ml); then a soln of KOH (6 g) in water (12 ml) was added. The mixture was refluxed under N_2 for 2 days and condensed *in vacuo* to remove excess EtOH. The condensed soln was neutralized with cold 3N–HCl and extracted with ether. The usual work-up gave dicarboxylic acid **3** (3.35 g, 66.3% yield from **18**) as an amorphous solid. The structure of **3** was confirmed by its conversion to the dimethyl ester: a colorless oil; ^{1}H-NMR δ 1.24–2.92 (10H, m), 3.67 (6H, s), and 6.04–6.20 (2H, m); IR ($CHCl_3$) 1720 cm^{-1}; (Found: M^+, 238.1205. $C_{13}H_{18}O_4$ Requires: M, 238.1205).

Condensation between meso-cis-5-*norbornene-endo*-2,3-*diacetic acid* (**3**) *and* 4(R)-MCTT

4(*R*)-MCTT (5.929 g, 32.907 mmol) and DCC (7.533 g, 36.041 mmol) were added to a soln of **3** (3.291 g, 15.67 mmol) in pyridine (30 ml). The mixture was stirred at room temp under N_2 for 7 days and a large amount of toluene was added. The solvent was evaporated off *in vacuo* to give an oily residue, to which was added EtOAc. The ppt (DCC urea) was filtered off and the filtrate was condensed *in vacuo* to give an oily residue, which was subjected to the flash column chromatography on silica gel with benzene to afford **19** (5.068 g, 62.1% yield) as a yellow oil. $[\alpha]_D^{20}$ – 164.12° (c = 3.74, $CHCl_3$); ^{1}H-NMR δ 1.36–1.50 (2H, m), 2.40–3.20 (10H, m), 3.35 (2H, dd, J = 11.7 and 2.2 Hz), 3.73 (1H, dd, J = 11.7 and 8.6 Hz), 3.75 (1H, dd, J = 11.7 and 8.6 Hz), 3.82 (6H, s), 5.50–5.70 (2H, m), and 5.96–6.24 (2H, m); IR ($CHCl_3$) 1759 and 1707 cm^{-1}; (Found: M^+, 528.0507. $C_{21}H_{24}N_2O_6S_4$ Requries: M, 528.0516).

Analysis of diamide **19** with piperidine

Piperidine (200 mg) was dissolved in CH_2Cl_2 (10 ml). The soln (4.4 ml) was dropwise added to a soln of **19** (535 mg, 1.013 mmol) in CH_2Cl_2 (40 ml) at – 78° under N_2 with stirring. After being stirred at – 78° for 2 hr, the mixture was evaporated *in vacuo* to give a yellow oily residue, which was checked by HPLC: column, JASCO Finepak SIL; solvent system, *n*-hexane–AcOEt (3:2); pressure, 130 kg/cm^2. Retention times: 7.52 min and 10.18 min for **20** and **21**, respectively. The residue was chromatographed by the flash technique on a silica gel column with benzene and then with benzene–AcOEt (9:1) to give a mixture (293 mg, 66.3% yield) as yellow crystals. Recrystallization of the mixture from n-hexane–CH_2Cl_2 afforded a sole pure compound (194 mg, 43.8% yield) as yellow needles. m.p. 130–130.5°; $[\alpha]_D^{20}$ – 108.04° (c = 0.83, $CHCl_3$); ^{1}H-NMR δ 1.20–3.80 (20H, m), 3.35 (1H, dd, J = 11.7 and 2.0 Hz), 3.72 (1H, dd, J = 11.7 and 8.6 Hz), 3.81 (3H, s), 5.67 (1H, dd, J = 8.6 and 2.0 Hz), and 5.96–6.24 (2H, m); IR ($CHCl_3$) 1755, 1703, and 1625 cm^{-1}; (Found: C, 57.77; H, 6.48; N, 6.42; M^+, 436. $C_{21}H_{28}O_4N_2S_2$ Requires: C, 57.57; H, 6.53; N, 6.38; M, 436).

Crystal data of amide **20**

$C_{21}H_{28}O_4N_2O_2$, orthorhombic, space group $P\,2_12_12_1$, $a = 10.258(1)$ Å, $b = 34.061(4)$ Å, $c = 6.153(1)$ Å, $Z = 4$. Intensities of 2143 reflections ($\theta_{max} = 65.0°$) were measured on a Rigaku diffractometer with graphitemonochromatized Cu Kα radiation ($\lambda = 1.54178$ Å). The structure was solved by direct methods and refined by the block-diagonal least-squares technique to R value of 0.046 and 1847 observed reflections.[19]

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[19]Atomic coordinates of compound **20** have been deposited with the Cambridge Crystallographic Data Center.