Highly Selective Nonenzymatic Chiral Induction into 3-Methylglutaric Acid and *cis*-4-Cyclohexen-1,2-ylenebis(acetic acid) Utilizing a Functional Five-Membered Heterocycle 4(*R*)-MCTT[1]

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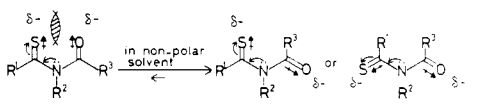
Diamide **8**, prepared by treatment of 3-methylglutaric acid (**1**) with 4(*R*)-MCTT (**5**) in the presence of DCC in pyridine, was subjected to aminolysis with 1 equiv of piperidine in CH_2Cl_2 at −30 °C to give a mixture of diastereomers **9a** and **10a** in a 88:12 ratio. Compound **9a**, separated by silica gel column chromatography, was treated with various nucleophiles to give optically pure bifunctional synthons **11a–k** in high yields. Highly selective chiral induction into *cis*-4-cyclohexen-1,2-ylenebis(acetic acid) (**4**) was also performed. Aminolysis of **19** with 1 mol equiv of piperidine gave a mixture of **20** and **21** with 94% selectivity of the former. Similar chiral induction into *cis*-cyclohexan-1,2-ylenebis(acetic acid) (**23**) was tried. Aminolysis of its 4(*R*)-MCTT diamide (**24**) with piperidine gave **25** and **26** in a 89:11 ratio; the opposite selectivity was obtained with **19**. The conformations of **19** and **24** in a solvent, the relationship between the susceptibility of their conformations and environmental temperature, and the diastereoselectivity of the reaction are discussed on the basis of the 400-MHz ^1H NMR spectra.

Optically active simple compounds are increasingly being used[3] as efficient chiral building blocks for the construction of optically active key intermediates in the total synthesis of biologically active natural products, such as macrolides,[4] macrolactams,[5] polyethers,[6] β-lactams,[7] peptides,[8] amino sugars,[9] and nucleotide[10] antibiotics and/or anticancer agents, prostaglandins,[11] and leukotrienes.[12] Therefore,

Scheme I



extensive studies are being conducted on chiral induction utilizing chemical,[3,13] enzymatic,[10a,13a,14] and microbiological methods[14c,15] and chemical degradation of readily available natural products.[4b,c,e,5,6a,b,7b,c,8,11b–d,16]

While most modern chemical chiral syntheses utilize metal chelation for molecule regulation, we tried to develop a new chiral design based on the symmetry of the organic molecules without using metal chelation.

Highly enantioselective differentiations between two identical ligands in prochiral σ-symmetric dicarboxylic acid esters have been done with microorganisms[14c,15a] or enzymes like α-chymotrypsin[14c,h] and pig liver esterase.[14a–g] Enzymatic discrimination between conformational enantiomers of *cis*-1,2-bis(hydroxymethyl)cyclohexane and the related diols has also been reported.[14d] Some nonenzymatic methods for distinguishing the prochiral ligands of 3-

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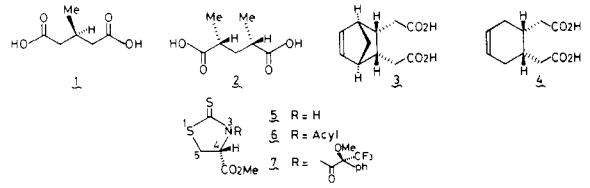
phenylglutaric anhydride have been reported, but they were unsatisfactory from the viewpoint of enantioselectivity.[17]

In a recent preliminary report, we described a highly regioselective differentiation between two identical groups in 3-methylglutaric acid (1).[18] We developed this method for meso compounds, enabling highly selective chiral induction into *meso*-2,4-dimethylglutaric acid (2)[19,20] and *meso*-5-norbornene-2,3-*endo*,*endo*-diacetic acid (3).



Here, we report the complete details of the design and chemical chiral induction to 3-methylglutaric acid (1) together with recent findings on highly diastereoselective chiral induction into *cis*-4-cyclohexen-1,2-ylenebis(acetic acid) (4).

Basic Strategy for the Chiral Design. We chose the prochiral σ-symmetric molecule 1 for the new chiral design because we wanted to (1) perform the enzymimic chiral recognition through a simple chemical procedure, (2) establish a new concept for chiral induction into the prochiral σ-symmetric molecule by using a chiral auxiliary, and (3) obtain the optically active product from 1 for further enantioconvergent reactions by suitable exchange of the functional groups because of its latent symmetry.[14c]

To regulate the free rotatory molecule in the transition state of chiral induction, we utilized the dipole–dipole repulsion between the carbonyl and the thiocarbonyl groups. The basic regulation system is illustrated in Scheme I. The thiocarbonyl group conjugating with the electron-donating atoms or groups, e.g., nitrogen atom, oxygen atom, the aromatic ring, and olefinic π-bond system, exhibits higher enhancement of the dipole moment than the corresponding carbonyl group.[21] Thus, 4(*R*)-(methoxycarbonyl)-1,3-thiazolidine-2-thione [4(*R*)-MCTT] (5) was selected as a chiral auxiliary. This five-membered heterocycle 5 is easily prepared in large quantities from the commercially available L-cysteine methyl ester hydrochloride and offers five merits for the chiral synthesis: (1) The fairly planar 1,3-thiazolidine-2-thione moiety can clearly differentiate the asymmetric environment of 4-(*R*)-MCTT (5). (2) Because of its excellent leaving property,[22] mild and smooth reaction of its 3-acyl derivatives can be expected at low temperature. (3) Since 4(*R*)-MCTT (5) and its 3-acyl derivative 6 show UV absorption [compound 5 279 nm (ϵ = 1.40 × 10^4, $CHCl_3$); compound 6 265–276 nm (ϵ = 1.32–1.50 × 10^4, $CHCl_3$), 304–316 nm (ϵ = 0.57–1.15 × 10^4, $CHCl_3$)], analysis of the chiral induction process should be easy by high performance liquid chromatography (HPLC) together with a UV detector. (4) Because 3-acyl derivatives 6 of 4(*R*)-MCTT (5) are yellow, their reactions with nucleophiles can be monitored by the color disappearance.[22] (5) The enantiomeric purity of 5 can be readily checked by HPLC and NMR (^1H and ^{19}F) analyses of its MTPA [α(*S*)-α-methoxy-α-(trifluoromethyl)phenylacetic acid] amide 7.[23]

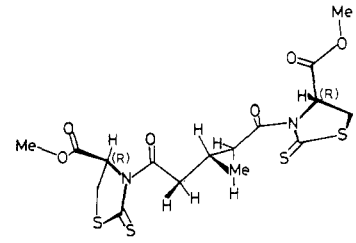
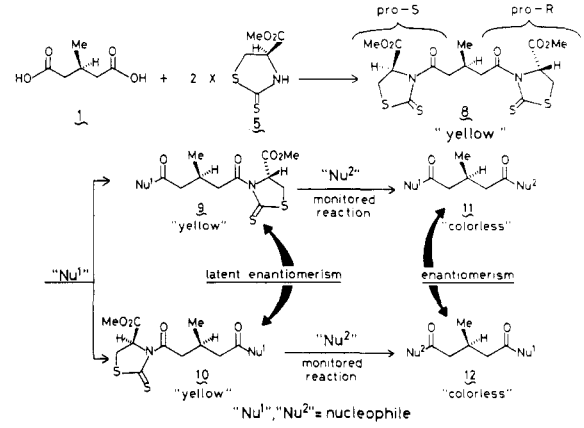


Figure 1. Perspective view of the crystallographic structure of compound 8.

Scheme II



Chiral Induction into 3-Methylglutaric Acid. First, we tried to attain highly regioselective differentiation between two identical groups in 3-methylglutaric acid (1). The sequential reaction process is illustrated in Scheme II.

The important key compound 8, 3-methylglutaric acid (1) diamide with 4(*R*)-MCTT (5), was designed as follows. In the molecule 8, the fairly strong dipole–dipole repulsion between the thiocarbonyl and the carbonyl groups[21] and the repulsion between the pro-*S* group and the pro-*R* group may regulate the stereochemistry of the compound to stabilize a favorable W-shape or a slightly twisted W-shape conformation especially at low temperature. In the hypothetical W-shaped structure 8, the α-face of the carbonyl group in the pro-*S* ligand should be the least hindered when compared with the other three faces; the β-face of the carbonyl group in the pro-*S* ligand is the most hindered by the β-methoxycarbonyl and β-methyl groups; the β-face of the carbonyl group in the pro-*R* ligand is hindered by the β-methyl group; the α-face of the carbonyl group in the pro-*R* ligand is hindered by the α-methoxycarbonyl group, but the said face is not hindered by either group, both of which are β-oriented. Therefore, a suitable nucleophile can predominantly attack the amide carbonyl group in the pro-*S* ligand from the least hindered α-face in the transition state.

The key diamide 8 was prepared and subjected to X-ray analysis[24] and its crystallographic structure was shown to have a slightly twisted W-shape conformation, supporting in principle our working hypothesis (Figure 1).

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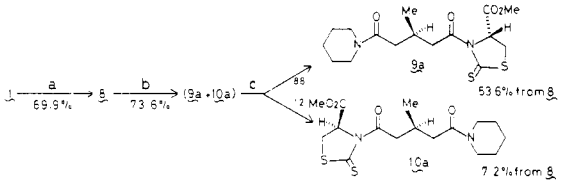
Table I. Search for a Useful Amine Nucleophile ("Nu^1")[a]

entry	"Nu^1"	ratio of diastereomers[b] at room temp	at −30 °C
1[c]	H_2N-CH_2–	(1 min)[f] 48.5:51.5	(1 h)[f] 50.5:49.5
2[d]	HN	(1 min) 66.9:33.1	(0.5 h) 78.4:21.6
3[d]	HN	(1 min) 72.2:27.8	(2 h) 86.9:13.1
4[d]	HN	(1 min) 71.5:28.5	(3.5 h) 84.7:15.3
5[e]	HN O	(1 min) 74.4:25.6	(13 h) 85.9:14.1
6[c]	HN	(4 h) 70.0:30.0	

[a] For the reaction conditions, see text. [b] The ratio was determined by HPLC analysis of the reaction mixture. Detection: UV (305 nm); column JASCOSIL SS-05-250(silica gel type); solvent benzene–AcOEt (5:1),[c] (2:1),[d] or (1:1).[e] [f] Reaction time.

Scheme III[a]



[a] a, 4(*R*)-MCTT (**5**) (2 mol equiv), DCC, pyridine; b, piperidine (1 mol equiv), CH_2Cl_2, −30 °C; c, silica gel column, hexane-Et_2O-EtOAc (2:2:1).

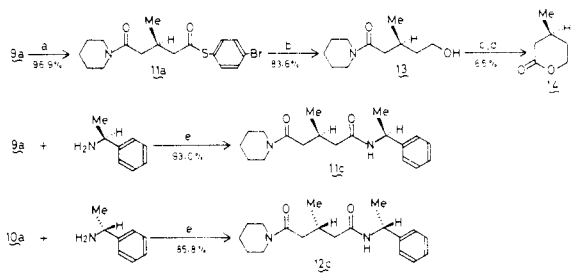
According to our hypothesis, the nucleophile ("Nu^1") may attack selectively from the α-side of the carbonyl group in the pro-*S* ligand to give compound **9** as a major product (see Scheme II). Separation of a mixture of diastereoisomers **9** and **10** should be easy, which is one of the merits of this diastereomeric-differentiating method over the corresponding enantiomeric-differentiating reactions (e.g., enzymatic chiral hydrolysis). The second attack of the other nucleophile ("Nu^2") may produce compound **11** from the major product **9** and compound **12** from the minor product **10**; **11** and **12** are enantiomers. Thus, highly regioselective differentiation between two identical groups (CH_2COOH) in 3-methylglutaric acid (**1**) should be achieved.

The key compound **8** was prepared as yellow needles (mp 113–114 °C) in 69.9% yield by treatment of 3-methylglutaric acid (**1**) with 2 mol equiv of 4(*R*)-MCTT (**5**) in the presence of DCC in pyridine. As a preliminary experiment, aminolysis of **8** was tried in CH_2Cl_2 with 1 mol equiv of various amines at room temperature or at −30 °C in order to find the best nucleophile "Nu^1" (Table 1). As expected, the ratio of the two diastereomers, checked by HPLC analysis, showed excellent regioselecitivity (78–87%) of cyclic secondary amines (entries 2–5 in Table I) especially at −30 °C. The best result was obtained with piperidine (entry 3), which was adopted as "Nu^1".

Compound **8** was subjected to aminolysis with 1 mol equiv of piperidine in CH_2Cl_2 at −30 °C. The mixture obtained was chromatographed on a silica gel column with hexane–Et_2O–EtOAc (2:2:1) to separate a pure major product **9a** as yellow needles (mp 95.5–96 °C) and a pure minor product as a yellow oil in a ratio of 88:12 (Scheme III).

To check the structure and absolute configuration of the major product, **9a** was allowed to react with *p*-bromobenzenethiol in the presence of NaH, and the thio ester **11a** (96.9% yield) obtained was reduced with $NaBH_4$ in aqueous THF, giving alcohol **13** in 83.6% yield. Acidic hydiolysis of this followed by lactonization gave compound **14** (65% yield), which proved to be identical with (−)-3-(*S*)-methylvalerolactone (**14**) (Scheme IV).[14f] Furthermore, aminolysis of **9a** with (−)-(*S*)-α-methylbenzylamine gave diamide **11c** in high yield (Scheme IV). The structure and stereochemistry of **11c** were established by X-ray analysis (Figure 2).[24] Thus, the structure and absolute configuration of the major product were confirmed to be **9a**, and our working hypothesis was proved to be correct. The structure and absolute configuration of the minor product **10a** were established by transforming it into diamide **12c**, the enantiomer of compound **11c**, via aminolysis with (+)-(*R*)-α-methylbenzylamine (Scheme IV).

Scheme IV[a]



[a] a, *p*-Bromobenzenethiol, NaH, THF; b, $NaBH_4$, aqueous THF; c, 6 N HCl, refluxing; d, benzene, azeotropic refluxing; e, CH_2Cl_2, room temperature.

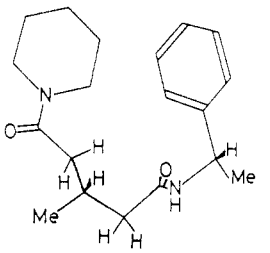
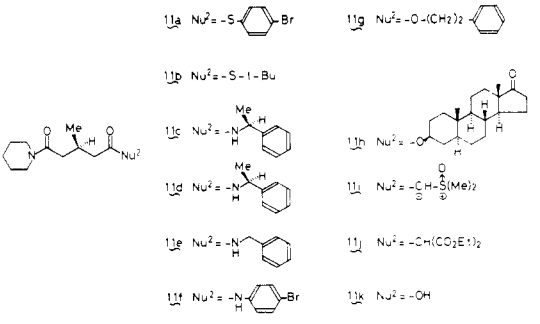


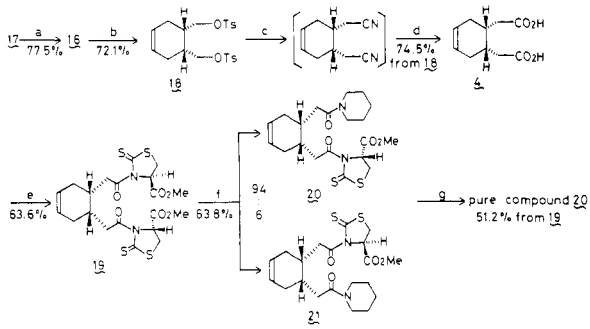
Figure 2. Perspective view of the crystallographic structure of compound **11c**.

The major product **9a** was subjected to "monitored reactions" with several nucleophiles "Nu^2". As can be seen from Table II, thio ester preparation (entries 1 and 2), aminolysis (entries 3–6), esterification (entries 7 and 8), C–C bond formation (entries 9 and 10), and hydrolysis (entry 11) proceeded smoothly to afford the corresponding optically pure compounds **11a–k** in high yields. Some of these optically pure products may be useful as bifunctional synthons for the total synthesis of biologically active natural products.



(24) Crystallographic details, tables of atomic positional, and thermal parameters are availabe as supplementary material of our preliminary communication.[18]

Scheme V[a]

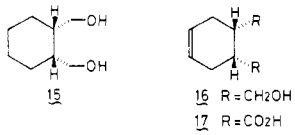


[a] a, $LiAlH_4$, THF; b, TsCl, pyridine; c, NaCN, Me_2SO, 90 °C; d, KOH, EtOH-H_2O, refluxing; e, 4(*R*)-MCTT (**5**) (2 mol equiv), DCC, pyridine; f, piperidine (1 mol equiv), THF, −78 °C; g, recrystallization from hexane-CH_2Cl_2.

This chemical chiral induction method is conceptually similar to the enzymatically enantioselective hydrolysis of 3-substituted glutaric acid esters with pig liver esterase[14e,g] and α-chymotrypsin.[14h]

Our work established the novel concept that the introduction of the two same chiral ligands, e.g., two 4(*R*)-MCTT groups, into a symmetrical molecule having a prochiral center changes its original symmetrical environment into an unsymmetrical one.

Chiral Induction into *cis*-4-Cyclohexen-1,2-ylenebis(acetic acid). As an application of this novel method, we attempted chiral induction into *cis*-4-cyclohexen-1,2-ylenebis(acetic acid) (**4**), which should have two extreme enantiomeric conformers **4a** and **4b** (Figure 5). As ring conversion of the cyclohexene part freely at room temperature, **4a** and **4b** cannot be resolved. Resolution of this type usually requires a particularly high barrier energy for the ring conversion at very low temperature.[25] Highly selective chiral induction into conformational enantiomers (*e.g.*, diols **15** and **16**) has been achieved via the enzyme discrimination procedure by Jones and his co-workers.[14d,25] However, chemical chiral induction into the conformational enantiomers had not been reported.



15 **16** R = CH_2OH **17** R = CO_2H

Compound **4** was derived from a commercially available dicarboxylic acid **17** via the sequence shown in Scheme V.[26] Usual treatment of **4** and 2 equiv of 4(*R*)-MCTT (**5**) with DCC in pyridine afforded diamide **19** (mp 128–128.5 °C) in 63.6% yield. Aminolysis of diamide **19** with 1 equiv of piperidine in THF at −78 °C gave a yellow solid (63.8% yield), which contained a 94.0:6.0 ratio of the products according to HPLC analysis. The solid mixture was recrystallized to give the major component (mp 125–125.5 °C) in overall 51.2% yield from **19** (Scheme V).

The structure and absolute stereochemistry of the major product were clarified to be **20** by crystallographic X-ray analysis.[27] A perspective view of the crystallographic structure of **20** is shown in Figure 3.[27]

As we expected **20** to be useful as "a bifunctional and optically active synthon" for asymmetric synthesis of biologically active compounds, such as prostacarvacyclins and coriolin derivatives, we established a new highly diastereoselective chiral method for recognizing the conformational enantiomers of *cis*-4-cyclohexen-1,2-ylenebis(acetic acid) (**4**). To better understand this method, the original key compound **19** was analyzed by X-ray.[27] The perspective view of one of the three molecules in the asymmetric unit of **19** is shown in Figure 4.[27] The amide group substituted on the C1(*R*) atom obviously occupied the equatorial position, while the amide substituent on the C2(*S*) atom was axially oriented. This perspective view of **19** is useful for the discussion of regio- and stereoselectivity of the reaction.

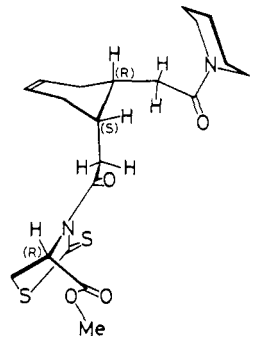


Figure 3. Perspective view of the crystallographic structure of compound **20**.

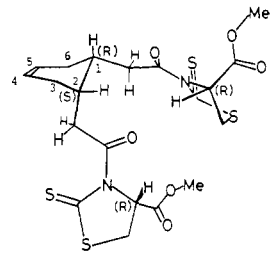


Figure 4. Perspective view of the crystallographic structure of compound **19**.

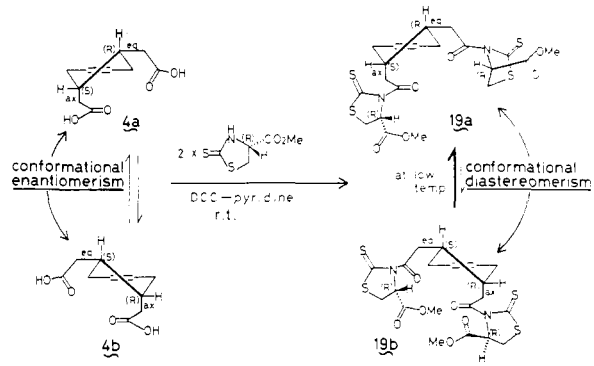


Figure 5. 4(*R*)-MCTT promoted discrimination between conformational enantiomers **4a** and **4b**.

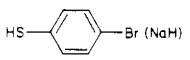
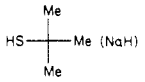
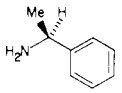
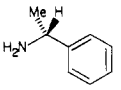
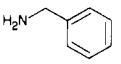
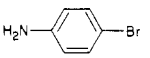
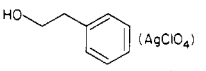
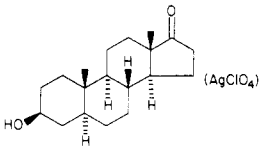
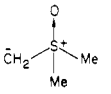
19a should be one of two possible diasteromeric conformers caused by the ring conversion (Figure 5). X-ray analysis showed that the key diamide **19** prepared from **4** had conformation **19a**.

Thus, chemical discrimination of **4a** from conformational enantiomers (**4a** and **4b**) was successfully achieved by their convergence onto **19a**. This 4(*R*)-MCTT-promoted discrimination between **4a** and **4b** should occur even in solution, especially at low temperature. In fact, the 400-MHz ^1H NMR study of **19** in THF supported an exclusive bias toward the preferred conformer **19a** (vide post).

The high stereoselectivity of the nucleophilic attack of piperidine can be discussed in terms of the preferable structure **19** shown in Figure 4. The speculative approach

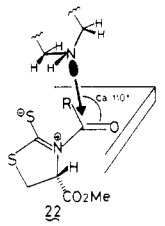
(25) Cf. Goodbrand, H. B., Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1977**, *469*.
(26) Bloomfield, J. J.; Fennessey, P. V. *Tetrahedron Lett.* **1964**, 2273.
(27) Crystallographic structures of compounds **19** and **20** and their data are available as supplementary material.

Table II. Monitored Reactions of Active Amide 9a with Various Nucleophiles ("Nu^{2n}")

entry	"Nu^{2n}"	product	mp, °C	$[\alpha]^{25}$, deg ($CHCl_3$)	yield,[a] %
1		**11a**	oil	−1.39 (*c* 1.73)	96.9
2		**11b**	oil	−4.02 (*c* 1.32)	85.4
3		**11c**	155–155.5	−63.48 (*c* 0.66)	93.0
4		**11d**	92–92.5	+51.67 (*c* 0.66)	88.7
5		**11e**	77–78.5	−2.90 (*c* 1.00)	98.0
6		**11f**	124–125	+0.98 (*c* 1.02)	99.0
7		**11g**	oil	−4.31[b] (*c* 2.67)	84.1
8		**11h**	124.5–125	+47.10[b] (*c* 1.00)	77.2
9		**11i**	130–131.5	+2.30 (*c* 1.00)	76.2
10	$CH_2(CO_2Et)_2$ (NaH)	**11j**[c]	oil	−3.63 (*c* 2.40)	98.5
11	H_2O (pyridine)	**11k**	68–69.5	−6.19[b] (*c* 4.54)	92.3

[a] Isolated yield. [b] $[\alpha]_D$ was determined at 22 °C (**11g** and **11h**) and at 23 °C (**11k**). [c] The product **11j** was a mixture of the keto and enol form in a 4:6 ratio (^1H NMR analysis).

of piperidine nucleophile ("PNu") from the least hindered side to the amide carbonyl group can be depicted as formula **22**.[28]



22

In structure **19** (Figure 6), the approach of "PNu" along arrow A to the β-face of the *R* site amide carbonyl group should be interferred by the β-oriented methoxycarbonyl group. Approach of the "PNu" along arrow D to the α-face of the *S* site amide carbonyl group would meet with similar interference from the α-oriented methoxycarbonyl group. "PNu" cannot approach along arrow C to the β-face of the *S* site amide carbonyl group because of steric hindrance between the C3-α quasi-equatorial and C2-β equatorial hydrogen atoms and the axially oriented hydrogen atoms of the "PNu". However, "PNu" might be able to approach along arrow B (the least sterically hindered course) to the α-face of the *R* site amide carbonyl group, basically as shown in formula **22**, because there is a sufficiently large cavity to accept the "PNu" in **19** (Figures 4 and 6).

Finally, we tried a similar chiral induction into *cis*-

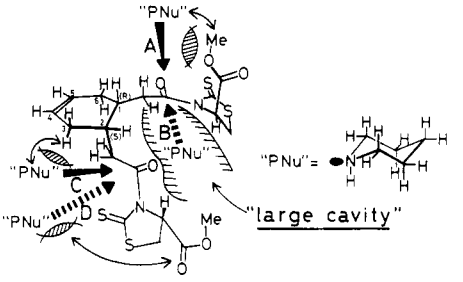
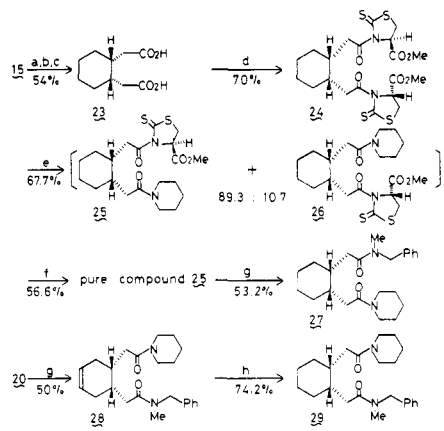


Figure 6.

cyclohexan-1,2-ylenebis(acetic acid) (**23**) for comparison with **19**. Aminolysis of diamide **24** derived from **23** and 4(*R*)-MCTT (**5**) with 1 equiv of piperidine in THF at −78 °C gave a diastereomeric mixture (67.7% yield) of **25** and **26** in a ratio 89.3:10.7 (HPLC analysis). Chromatographic separation of the mixture on a silica gel column with benzene gave the major product **25** in 56.6% yield from **24**. Its structure and absolute stereochemistry were determined by chemical correlation with compound **25** which was subjected to monitored aminolysis with 1 equiv of *N*-benzyl-*N*-methylamine in THF to give diamide **27**, which was an enantiomer of diamide **29** derived from the known compound **20** via **28**. Therefore, the structure and absolute stereochemistry of the major product from aminolysis of **24** could be represented by **25**. This means that the "PNu" predominantly attacked the *R* site amide carbonyl group. This interesting difference of chiral recognition by "PNu" between cases **19** and **24** should be studied further.

(28) Bürgi, H. B.; Dunitz, J. D.; Lehn, J. M.; Wipff, G. *Tetrahedron* **1974**, *30*, 1563.

Scheme VI[a]



[a] a, TsCl, pyridine; b, NaCN, Me_2SO, 90 °C; c, KOH, EtOH–H_2O, refluxing; d, 4(*R*)-MCTT (**5**) (2.1 mol equiv), DCC, pyridine; e, piperidine (1 mol equiv), THF, −78 °C; f, silica gel column, benzene; g, benzylmethylamine (1.1 mol equiv), THF; h, H_2, Pd-C, EtOH.

The 400-MHz ^{1}H NMR spectra of diamide **19** and **24** were determined in THF-d_8 at 28, 0, and −20 °C, respectively.[29] On the basis of the perspective view (Figure 4) of **19**, we might be able to assign all peaks of the two kinds of methylenes, the *R* site equatorial CH_2 and the *S* site axial CH_2.[30] The ^{1}H NMR of **19** in THF-d_8 at −20 °C showed two sets of double doublet peaks and ABX-type peaks in which H^A and H^B were located apart from each other: the peaks at δ 2.99 (1 H, dd, J = 17.1 and 9.3 Hz) and 3.41 (1 H, dd, J = 17.1 and 3.4 Hz) are assignable to the *R* site equatorial CH_2 and the peaks at δ 3.19 (1 H, part A of ABX-type peaks, J_{AB} = 17.6 Hz, J_{AX} = 5.4 Hz) and 3.32 (1 H, part B of ABX-type peaks, J_{AB} = 17.6 Hz, J_{BX} = 7.8 Hz) are assignable to the *S* site axial CH_2. On the other hand, the spectrum of **19** which was determined at 28 °C had two sets of double doublet peaks and ABX-type peaks in which H^A and H^B were located fairly close to each other: the peaks at δ 3.04 (1 H, dd, J = 16.6 and 8.8 Hz) and 3.44 (1 H, dd, J = 16.6 and 4.4 Hz) are assignable to the *R* site equatorial CH_2 and the peaks at 3.24 (1 H, part A of ABX-type peaks, J_{AB} = 17.6 Hz, J_{AX} = 5.9 Hz) and 3.30 (1 H, part B of ABX-type peaks, J_{AB} = 17.6 Hz, J_{BX} = 7.3 Hz) are assignable to the *S* site axial CH_2.

In the case of diamide **24**, no such temperature dependence of the ABX-type peaks as those of **19** was recognized. The peak patterns [δ 3.07 (1 H, dd, J = 16.6 and 8.3 Hz), 3.37 (1 H, dd, J = 16.6 and 4.9 Hz), 3.23 (1 H, part A of ABX-type peaks, J_{AB} = 17.6 Hz, J_{BX} = 6.3 Hz), 3.27 (1 H, part B of ABX-type peaks, J_{AB} = 17.6 Hz, J_{BX} = 6.3 Hz)] of the methylene region at 0 °C were similar to those found at 28 °C [δ 3.10 (1 H, dd, J = 16.6 and 8.3 Hz), 3.36 (1 H, dd, J = 16.6 and 4.4 Hz), 3.24 (1 H, part A of ABX-type peaks, J_{AB} = 17.6 Hz, J_{AX} = 6.8 Hz), and 3.28 (1 H, part B of ABX-type peaks, J_{AB} = 17.6 Hz, J_{BX} = 6.8 Hz)]. Although, the peak pattern chiral the methylene region of the spectrum at −20 °C was not very clear, it was similar to that obtained at 28 °C.

These findings suggested that the *S* site CH_2 in **19** is very susceptible to the environmental temperature because of the free rotatory flexibility of its C_2–CH_2 axial bond. In **24**, the conformation of both the C_1–$CH_2CON<$ and C_2–$CH_2CON<$ groups is probably fixed by the steric hindrance between the hexane ring axial C–H bonds and the axial C–CH_2 bond, and thus the peaks of these two methylene sets are not as sensitive to temperature. Therefore, we tried the chrial aminolysis of **19** and **24** with 1 equiv of piperidine each at room temperature. Interestingly, while selectivity greatly decreased with **19** (**20**:**21** = 50.9:49.1) in comparison with the reaction at −78 °C, high selectivity was retained with **24** even at room temperature (**25**:**26** = 84.2:15.8). These results support our interpretation of the 400-MHz ^{1}H NMR experiments on **19** and **24**.

Our method is a novel and simple nonenzymatic procedure for highly selective chiral induction into *cis*-4-cyclohexen-1,2-ylenebis(acetic acid) utilizing 4(*R*)-MCTT-promoted discrimination of conformational enantiomers. This procedure may provide the means for better understanding of enzymatic reactions.

Experimental Section

Melting points were determined with a Yanagimoto microapparatus. IR spectra were recorded on a JASCO A-202 spectrophotometer and UV spectra were recorded on a JASCO UVIDEC-610 spectrophotometer. Optical rotations were measured on JASCO DIP-181 and Perkin-Elmer 241 polarimeters. Mass spectra were recorded on JEOL JMS-DX 300 and Hitachi M-80 mass spectrometers. ^{1}H NMR and ^{13}C NMR spectra were determined in $CDCl_3$ with JEOL JMN-FX100 (100 MHz), JEOL-FX270 (270 MHz), and JEOL-JX400 (400 MHz) spectrometers;signals are given in ppm from $SiMe_4$ as internal standard. High performance liquid chromatography was determined by JASCO Tri Rotar (UV-100) and JASCO Tri Rotar SR 2 equipped with JASCO DP-L220 LC-data processor. Extracts were dried over anhydrous Na_2SO_4. Merck silica gel (Kiesel gel 60H) was used for flash column chromatography.

4(*R*)-(Methoxycarbonyl)-1,3-thiazolidine-2-thione (5). To a solution of L-cysteine methyl ester hydrochloride (8.58 g, 50 mmol) and CS_2 (4.5 mL, 75 mmol) in CH_2Cl_2 (200 mL) was added Et_3N (13.9 mL, 100 mmol) with stirring under ice cooling. After being stirred at room temperature for 44 h, the reaction mixture was washed with an aqueous solution saturated with $(NH_4)_2SO_4$, dried over anydrous Na_2SO_4, and evaporated in vacuo to give an oily residue. The residue was purified on a silica gel column with $CHCl_3$ to afford compound **5** (7.71 g, 87.1% yield) as a colorless oil: $[\alpha]^{21}_D$ −67.00° (*c* 1.10, $CHCl_3$); ^{1}H NMR (100 MHz) δ 3.82 (1 H, d, J = 6.6 Hz), 3.85 (1 H, d, J = 8.1 Hz), 3.86 (3 H, s), 4.94 (1 H, dd, J = 6.6 and 8.1 Hz), 7.4–8.5 (1 H, br); IR ($CHCl_3$) 1747 cm^{-1}; UV ($CHCl_3$) 279 nm (ε 1.4 × 10^4); MS, *m*/*e* 177 (M^+). Anal. Calcd for $C_5H_7NO_2S_2$: C, 33.91; H, 3.98; N, 7.91. Found: C, 33.85; H, 3.89; N, 7.85.

Preparation of 3-Methylglutaric Acid 4(*R*)-MCTT Diamide (8). A mixture of 3-methylglutaric acid (**1**) (5.54 g, 40 mmol), 4(*R*)-MCTT (**5**) (14.18 g, 80 mmol), DCC (18.16 g, 88 mmol), and pyridine (100 mL) was stirred at room temperature for 6 days. After evaporating the excess solvent in vacuo, the obtained residue was treated with benzene (150 mL) and then the precipitate (DC urea) was filtered off. The filtrate was condensed in vacuo to give 50 mL of solution, which was subjected to the flash chromatography on a short silica gel column with benzene–AcOEt (10:1) to afford diamide **8** (13.0 g, 69.8% yield) as yellow needles (from AcOEt–ether): mp 113–114 °C; $[\alpha]^{26}_D$ −163.90° (*c* 1.00, AcOEt); ^{1}H NMR (100 MHz) δ 1.08 (3 H, d, J = 6.6 Hz), 2.73 (1 H, m), 3.1–3.7 (4 H, m), 3.3–3.46 (2 H, m), 3.7 (2 H, m), 3.82 (6 H, s), 5.62 (2 H, m); ^{13}C NMR (67.80 MHz, room temperature) δ 20.3 (q, CH_3), 27.1 (d, CH), 31.0 (t, CH_2S), 31.1 (t, CH_2S), 44.2 (t, CH_2), 44.4(t, CH_2), 53.3 (q, OCH_3), 67.3(d, *C*HN), 67.4 (d, CH_2N), 168.9 (s, *C*OO), 173.0 (s, NCOC), 173.2 (s, NCOC), 200.2 (s, NCSS) 200.3 (s, NCSS); IR (KBr) 1755, 1740, 1702, 1693 cm^{-1}; MS, *m*/*e* 464 (M^+). Anal. Calcd for $C_{16}H_{20}N_2O_6S_4$: C, 41.38; H, 4.35; N, 6.03; S, 27.61. Found: C, 41.36; H, 4.32; N, 5.83; S, 27.48.

General Procedure of Search for Useful Amine Nucleophile (Nu^1): Diamide **8** (93 mg, 0.2 mmol) was treated with 0.2 mmol of each corresponding amine (see Table I) in CH_2Cl_2 (5 mL in the case at room temperature or 15 mL in the case at −30 °C) at room temperature or at −30 °C and the reaction mixture was

(29) The 400-MHz ^{1}H NMR spectra of the methylene (–$CH_2CON<$) region of diamide **19** and **24** are available as supplementary material.

(30) The relationship of coupling of methylene protons was confirmed by the proton decoupling experiments.

(31) Kunieda, T.; Witkop, B. *J. Am. Chem. Soc.* **1971**, *93*, 3487.

stirred for suitable time which was set by the monitored aminolysis of **8** with 2.1 mol equiv of amine. All reactions were checked by HPLC (see foot notes of Table I).

Aminolysis of Diamide 8 with Piperidine: A solution of piperidine (1.83 g, 21.5 mmol) in CH_2Cl_2 (30 mL) was dropwise added to a solution of compound **8** (10 g, 21.5 mmol) over 15 min under dry ice–acetone cooling and the mixture was stirred at −30 °C for 4 h. Evapolation of the solvent in vacuo gave a yellow residue which was chromatographed on silica gel eluting successively with benzene–AcOEt (30:1) and benzene–AcOEt (3:1). The starting compound **8** (1.31 g, 13.1% recovery) and 4(*R*)-MCTT (**5**) were recovered from the fractions obtained by the benzene–AcOEt (30:1) elution. A mixture (5.9 g, 73.6% yield) of **9a** and **10a** was obtained from the fractions of the benzene–AcOEt (3:1) elution. The mixture of diastereoisomers **9a** and **10a** was successfully separated by the flash chromatography on a silica gel column with hexane–ether–AcOEt (2:2:1 v/v). The first eluate gave compound **9a** (4.3 g, 53.6% yield from **8**) as yellow needles (from AcOEt–ether): mp 95.5–96 °C; $[\alpha]^{26}_D$ −106.4° (*c* 1.01, $CHCl_3$); ^1H NMR (100 MHz) δ 1.05 (3 H, d, *J* = 6.4 Hz), 1.3–1.7 (6 H, br m), 2.05–2.8 (3 H, m), 3.05–3.65 (6 H, m), 3.35 (1 H, dd, *J* = 11.2 and 2.2 Hz), 3.75 (1 H, dd, *J* = 11.2 and 8.3 Hz), 5.62 (1 H, dd, *J* = 8.3 and 2.2 Hz); IR (KBr) 1742, 1697, 1623 cm^{-1}; MS, *m/e* 372 (M^+). Anal. Calcd for $C_{16}H_{24}N_2O_4S_2$: C, 51.60; H, 6.50; N, 7.52; S, 17.22. Found: C, 51.41; H, 6.62; N, 7.47; S, 17.37.

The second eluate afforded compound **10a** (0.58 g, 7.2% yield from **8**) as a yellow oil: $[\alpha]^{18}_D$ −84.67° (*c* 1.54, $CHCl_3$); ^1H NMR (100 MHz) δ 1.05 (3 H, d, *J* = 6.4 Hz), 1.3–1.7 (6 H, m), 2.2–2.8 (3 H, m), 3.2–3.6 (6 H, m), 3.35 (1 H, dd, *J* = 11.7 and 2.0 Hz), 3.74 (1 H, dd, *J* = 11.7 and 8.6 Hz), 3.82 (3 H, s), 5.61 (1 H, dd, *J* = 8.6 and 2.0 Hz); IR ($CHCl_3$) 1745, 1700, 1619 cm^{-1}; MS, *m/e* 372 (M^+). Anal. Calcd for $C_{16}H_{24}N_2O_4S_2 \cdot {}^1/_2\ H_2O$: C, 50.39; H, 6.61; N, 7.34. Found: C, 50.13; H, 6.52; N, 7.23.

***S*-*p*-Bromophenyl 3(*R*)-Methyl-5-oxo-5-(1-piperidyl)pentanethioate (11a).** A solution of *p*-bromobenzenethiol (189 mg, 1 mmol) in THF (2 mL) was added to a suspension of 50% NaH (coated with mineral oil) (48 mg, 1 mmol) in THF (3 mL) under N_2. After being stirred at room temperature for 10 min, the mixture was treated with glacial acetic acid (0.15 mL) and the solvent was removed in vacuo to give an oily residue. The residue was subjected to the usual flash column chromatography with hexane and hexane–AcOEt (4:1) to give an oily residue which was further purified by distillation with a kugelrohr apparatus to give thio ester **11a** (185 mg, 96.9% yield) as a colorless oil: bp 200–210 °C (3 mm) (kugelrohr); $[\alpha]^{25}_D$ −1.39° (*c* 1.73, $CHCl_3$); ^1H NMR (100 MHz) δ 1.07 (3 H, d, *J* = 6.1 Hz), 1.3–1.75 (6 H, m), 2.1–3.0 (5 H, m), 3.3–3.7 (4 H, m), 7.18–7.58 (4 H, m); IR ($CHCl_3$) 1703, 1622 cm^{-1}. Anal. Calcd for $C_{17}H_{22}NO_2SBr$: C, 53.13; H, 5.77; N, 3.64; S, 8.34. Found: C, 52.90; H, 5.97; N, 3.91; S, 8.33.

3(*S*)-Methyl-5-oxo-5-(1-piperidyl)pentan-1-ol (13). To a solution of compound **11a** (376 mg, 0.98 mmol) in THF (5 mL) was added a solution of $NaBH_4$ (111 mg, 2.93 mmol) in MeOH (10 mL) under ice cooling and the mixture was stirred under the similar condition for 30 min. After being stirred at room temperature further for 1 h, the reaction mixture was treated as usual to give alcohol **13** (163 mg, 83.6 %) as a colorless oil: $[\alpha]^{28}_D$ −8.47° (*c* 1.63, $CHCl_3$); ^1H NMR (100 MHz) δ 1.00 (3 H, d, *J* = 6.6 Hz), 1.3–1.8 (8 H, m), 2.1–2.44 (3 H, m), 3.3 (1 H, br), 3.3–3.8 (6 H, m); IR ($CHCl_3$) 1614 cm^{-1}; MS, *m/e* 199 (M^+). Anal. Calcd for $C_{11}H_{21}NO_2 \cdot {}^1/_4H_2O$: C, 64.83; H, 10.62; N, 6.87. Found: C, 64.82; H, 10.88; N, 6.84.

3(*S*)-Methylvalerolactone (14). A mixture of compound **13** (400 mg, 2.01 mmol) and 6 N HCl (4 mL) was refluxed for 2 h and then benzene (30 mL) was added. The mixture was azeotropically refluxed adding water sometimes. After a precipitate was filtered off, the filtrate was evaporated in vacuo to give an oily residue. Distillation of the residue with a kugelrohr apparatus gave compound **14** (141 mg, 65.1% yield) as a colorless oil: $[\alpha]^{27}_D$ −26.18° (*c* 0.88, $CHCl_3$) [lit.[14f] $[\alpha]^{27}_D$ −24.8° (*c* 5.6, $CHCl_3$)]; ^1H NMR (100 MHz) δ 1.06 (3 H, d, *J* = 6.6 Hz), 1.32–2.34 (4 H, m), 2.44–2.88 (1 H, m), 4.08–4.56 (2 H, m); IR ($CHCl_3$) 1731 cm^{-1}. Anal. Calcd for $C_6H_{10}O_2 \cdot {}^1/_{10}H_2O$: C, 62.16; H, 8.87. Found: C, 62.25; H, 8.85.

3(*S*)-Methyl-1-[(1(*S*)-methylbenzyl)amino]-5-(1-piperidyl)pentane-1,5-dione (11c). (*S*)-(α-Methylbenzyl)amine (110 mg, 0.91 mmol) was added to a yellow solution of compound **9a** (300 mg, 0.81 mmol) in CH_2Cl_2 (10 mL). The mixture was stirred at room temperature for 15 min (the original yellow color of **9a** disappeared) and the solvent was evaporated in vacuo to give an oily residue. The residue was purified by the flash technique on a silica gel column with hexane–AcOEt (1:1) and $CHCl_3$–MeOH (10:1) to give compound **11c** (237 mg, 93.0% yield) as colorless needles (from AcOEt): mp 155–155.5 °C; $[\alpha]^{25}_D$ −63.48° (*c* 0.66, $CHCl_3$); ^1H NMR (100 MHz) δ 1.02 (3 H, d, *J* = 5 Hz), 1.48 (3 H, d, *J* = 6.8 Hz), 1.4–1.7 (6 H, m), 2.0–2.7 (5 H, m), 3.25–3.65 (4 H, m), 5.12 (1 H, m), 6.84 (1 H, br), 7.1–7.4 (5 H, m); IR (KBr) 1665, 1614 cm^{-1}; MS, *m/e* 316 (M^+). Anal. Calcd for $C_{19}H_{28}N_2O_2$; C, 72.11; H, 8.92; N, 8.85. Found: C, 71.93; H, 9.18; N, 8.75.

3(*R*)-Methyl-1-[(1(*R*)-methylbenzyl)amino]-5-(1-piperidyl)pentane-1,5-dione (12c). (*R*)-α-Methylbenzylamine (39 mg, 0.32 mmol) was added to a yellow solution of **10a** (107 mg, 0.29 mmol) in CH_2Cl_2 (5 mL). After being stirred at room temperature for 30 min, the reaction mixture was subjected to the usual workup to give compound **12c** (78 mg, 85.8%) as colorless needles (from AcOEt): mp 155–155.5 °C; $[\alpha]^{23}_D$ +63.19° (*c* 0.69, $CHCl_3$); ^1H NMR (100 MHz) δ 1.02 (3 H, d, *J* = 5.1 Hz), 1.48 (3 H, d, *J* = 6.8 Hz), 1.4–1.7 (6 H, m), 2.0–2.7 (5 H, m), 3.25–3.65 (4 H, m), 5.12 (1 H, m), 6.84 (1 H, br), 7.1–7.4 (5 H, m); IR (KBr) 1665, 1614 cm^{-1}; MS, *m/e* 316 (M^+). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 72.10; H, 9.14; N, 8.97.

***S*-*tert*-Butyl 3(*R*)-Methyl-5-oxo-5-(1-piperidyl)pentanethioate (11b).** A solution of 1,1-dimethylethanethiol (300 mg, 3.33 mmol) in THF (2 mL) was added to a suspension of 50% NaH (coated with mineral oil) (129 mg, 2.7 mmol) in THF (2 mL) under N_2. After being stirred at room temperature for 2 h, the reaction mixture was subjected to a workup similar to that used in the case of compound **11a** to afford thio ester **11b** (327 mg, 85.4 %) as a colorless oil: bp 155–160 °C (3 mm) (kugelrohr); $[\alpha]^{25}_D$ −4.02° (*c* 1.32, $CHCl_3$); ^1H NMR (100 MHz) δ 1.03 (3 H, d, *J* = 5.6 Hz), 1.45 (9 H, s), 1.4 (4 H, m); IR ($CHCl_3$) 1670, 1619 cm^{-1}; MS, *m/e* 285 (M^+). Anal. Calcd for $C_{15}H_{27}NO_2S$: C, 63.13; H, 9.54; N, 4.91; S, 11.22. Found: C, 62.72; H, 9.80; N, 4.73; S, 11.24.

3(*S*)-Methyl-1-[(1(*R*)-methylbenzyl)amino]-5-(1-piperidyl)pentane-1,5-dione (11d). This compound (226 mg, 88.7% yield) was prepared from **9a** (300 mg, 0.81 mmol) and (*R*)-α-methylbenzylamine (110 mg, 0.91 mmol) by the same procedure as in the case of **11c**. Compound **11d**: colorless needles from ether–hexane; mp 92–92.5 °C; $[\alpha]^{25}_D$ +51.67° (*c* 0.66, $CHCl_3$); ^1H NMR (100 MHz) δ 1.05 (3 H, d, *J* = 5.4 Hz), 1.48 (3 H, d, *J* = 6.8 Hz), 1.59 (6 H, br), 2.0–2.5 (5 H, m), 3.25–3.65 (4 H, m), 5.13 (1 H, m), 6.7 (1 H, br), 7.23–7.36 (5 H, m); IR (KBr) 1667, 1609 cm^{-1}; MS, *m/e* 316 (M^+). Anal. Calcd for $C_{19}H_{28}N_2O_2$: C, 72.11; H, 8.92; N, 8.85. Found: C, 71.93; H, 9.09; N, 8.74.

1-(Benzylamino)-3(*S*)-methyl-5-(1-piperidyl)pentane-1,5-dione (11e). This compound (159 mg, 98.0% yield) was prepared from **9a** (200 mg, 0.54 mmol) and benzylamine (63 mg, 0.59 mmol) by the usual manner (reaction time, 5 min). Compound **11e**: colorless needles from ether; mp 77–78.5 °C; $[\alpha]^{25}_D$ −29.0° (*c* 1.00, $CHCl_3$); ^1H NMR (100 MHz) δ 1.06 (3 H, d, *J* = 4.9 Hz), 1.3–1.7 (6 H, br), 2.0–2.6 (5 H, m), 3.25–3.60 (4 H, m), 4.43 (2 H, d, *J* = 5.9 Hz), 6.82 (1 H, br), 7.29 (5 H, m); IR (KBr) 1625 cm^{-1}; MS, *m/e* 302 (M^+). Anal. Calcd for $C_{18}H_{26}N_2O_2$: C, 71.49; H, 8.67; N, 9.26. Found: C, 71.20; H, 8.80; N, 9.24.

1-(*p*-Bromoanilino)-3(*S*)-methyl-5-(1-piperidyl)pentane-1,5-dione (11f). A mixture of **9a** (250 mg, 0.67 mmol), *p*-bromoaniline (122 mg, 0.71 mmol), and benzene (15 mL) was refluxed for 15 h and the solvent was evaporated in vacuo to give an oily residue. The residue was subjected to the flash column chromatography on silica gel with hexane–AcOEt (3:1) to afford **11f** (260 mg, 99.0% yield) as colorless needles (from ether–hexane): mp 124–125 °C; $[\alpha]^{25}_D$ +0.98 (*c* 1.02, $CHCl_3$); [1] NMR (100 MHz) δ 1.13 (3 H, br), 1.6–1.8 (6 H, br), 2.2–2.6 (5 H, m), 3.3–3.7 (4 H, m), 7.33–7.58 (4 H, m), 9.65 (1 H, br); IR (KBr) 1684, 1605 cm^{-1}. Anal. Calcd for $C_{17}H_{23}N_2O_2Br$: C, 55.60; H, 6.32; N, 7.62; Br, 21.74. Found: C, 55.49; H, 6.22; N, 7.50; Br, 21.76.

β-Phenylethyl 3(*R*)-Methyl-5-oxo-5-(1-piperidyl)pentanoate (11g). β-Phenylethyl alcohol (180 mg, 1.47 mmol) and **9a** (500 mg, 1.34 mmol) were added to benzene (15 mL) and then a solution of silver perchlorate (293 mg, 1.41 mmol) in THF (5 mL) was added. The mixture was stirred at room temperature for 1 h under N_2 and the precipitate was filtered off. The filtrate

was washed with aqueous solution saturated with $NaHCO_3$ and with brine, dried, and evaporated in vacuo to give an oily residue. Distillation of the residue with a kugelrohr apparatus afforded compound **11g** (267 mg, 84.1%) as a colorless oil: bp 200 °C (0.6 mm) (kugelrohr); $[\alpha]^{22}_D$ −4.31° (*c* 2.6, $CHCl_3$); ^1H NMR (100 MHz) δ 0.98 (3 H, d, *J* = 5.4 Hz), 1.3–1.7 (6 H, br), 2.0–2.5 (5 H, m), 2.91 (2 H, t, *J* = 7.1 Hz), 3.2–3.6 (4 H, m), 4.28 (2 H, t, *J* = 7.1 Hz), 7.0–7.32 (5 H, m); IR ($CHCl_3$) 1727, 1620 cm^{-1}; MS, *m/e* 317 (M^+). Anal. Calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.80; H, 8.72; N, 4.81.

***epi*-Androsterone Ester of 3(*R*)-Methyl-5-oxo-(1-piperidyl)pentanoic Acid (11h).** This compound (130 mg, 77.2% yield) was similarly prepared from **9a** (559 mg, 1.5 mmol), *epi*-androsterone (436 mg, 1.5 mmol), and a solution of $AgClO_4$ (311 mg, 1.5 mmol) in THF (2.5 mL) as in the case of **11g** (reaction time, 2 h). Compound **11h**: colorless prisms from ether–hexane; mp 124.5–125 °C; $[\alpha]^{22}_D$ +47.10° (*c* 1.00, $CHCl_3$); ^1H NMR (100 MHz) δ 0.85 (6 H, s), 1.02 (3 H, d, *J* = 5.6 Hz), 0.6–2.6 (33 H, m), 3.3–3.7 (4 H, m), 4.7 (1 H, m); IR (KBr) 1734, 1627 cm^{-1}; MS, *m/e* 485 (M^+). Anal. Calcd for $C_{30}H_{47}NO_4$: C, 74.18; H, 9.75; N, 2.88. Found: C, 74.42; H, 9.85; N, 2.66.

Dimethyloxosulfonium [3(*S*)-Methyl-5-(1-piperidyl)-1,5-oxopent-1-yl]methylide (11i). A mixture of trimethyloxosulfonium chloride (257 mg, 2 mmol),[31] 50% NaH (coated with mineral oil) (72 mg, 1.5 mmol), and THF (3 mL) was refluxed under N_2 for 2 h. To this suspension was added a solution of compound **9a** (186 mg, 0.5 mmol) at room temperature. After being stirred for 10 min, the reaction mixture was subjected to the usual workup to afford compound **11i** (109 mg, 76.0% yield) as colorless needles (from AcOEt–ether): mp 130–131.5 °C; $[\alpha]^{25}_D$ +2.30° (*c* 1.00, $CHCl_3$); ^1H NMR (100 MHz) δ 1.01 (3 H, d, *J* = 5.9 Hz), 1.4–1.7 (6 H, br), 2.0–2.6 (5 H, m), 3.40 (6 H, s), 3.3–3.6 (4 H, m), 4.45 (1 H, s); IR (KBr) 1622 cm^{-1}; MS, *m/e* 287 (M^+). Anal. Calcd for $C_{14}H_{25}NO_3S$: C, 58.51; H, 8.77; N, 4.87; S, 11.14. Found: C, 58.33; H, 8.91, N, 4.79; S, 10.94.

1,1-Bis(ethoxycarbonyl)-4(*S*)-methyl-6-(1-piperidyl)hexane-2,6-dione (11j). A solution of ethyl malonate (320 mg, 2 mmol) in THF (1 mL) was added to a suspension of 50% NaH (coated with mineral oil) (72 mg, 1.5 mmol) in THF (2 mL) and the mixture was stirred at room temperature under N_2 for 1 h. To this mixture was added a solution of **9a** (372 mg, 1 mmol) in THF (3 mL). After being stirred at room temperature for 1 h, the reaction was quenched by adding glacial acetic acid (0.12 mL). The mixture was treated as usual to give compound **11j** (350 mg, 98.5% yield) as a colorless oil: $[\alpha]^{25}_D$ −3.63° (*c* 2.40, $CHCl_3$); ^1H NMR (100 MHz) δ 1.02 (3 H, d, *J* = 5.9 Hz), 1.29, 1.31 (6 H, each t, *J* = 7.3 Hz), 1.4–1.7 (6 H, br), 2.1–2.9 (5 H, m), 3.3–3.6 (4 H, m), 4.26 (4 H, q), 4.52 (0.4 H, s, keto form H), 13.35 (0.6 H, s, enol form H); IR ($CHCl_3$) 1716, 1622 cm^{-1}; MS, *m/e* 355 (M^+). Anal. Calcd for $C_{18}H_{29}NO_6$: C, 60.82; H, 8.22; N, 3.94. Found: C, 60.82; H, 8.41; N, 4.06.

3(*R*)-Methyl-5-oxo-5-(1-piperidyl)pentanoic Acid (11k). Compound **9a** (500 mg, 2.8 mmol) was dissolved in pyridine (5 mL) and water (5 mL) was added. The mixture was stirred at room temperature for 15 h and the solvent was evaporated in vacuo to give an oily residue, which was subjected to the usual workup to afford carboxylic acid **11k** (264 mg, 92.3% yield) as colorless needles (from ether): mp 68–69.5 °C; $[\alpha]^{23}_D$ −6.19° (*c* 4.54, $CHCl_3$); ^1H NMR δ 1.08 (3 H, br), 1.4–1.8 (6 H, br), 2.2–2.6 (5 H, m), 3.3–3.7 (4 H, m), 11.05 (1 H, br); IR (KBr) 2450 (br), 1705, 1575 cm^{-1}; MS, *m/e* 213 (M^+). Anal. Calcd for $C_{11}H_{19}NO_3$: C, 61.94; H, 8.98; N, 6.57. Found: C, 61.86; H, 9.08; N, 6.47.

Reduction of *cis*-4-Cyclohexen-1,2-ylenebis(formic acid) (17). A solution of **17** (35.086 g, 0.2064 mol) in THF (300 mL) was dropwise added to a solution of $LiAlH_4$ (10.420 g, 0.2742 mol) in THF (200 mL) with stirring under ice cooling. After being stirred at room temperature overnight, the reaction was quenched with cold water (40 mL) and cold 15% NaOH (10 mL). The mixture was stirred for 30 min and the precipitate was filtered off. The filtrate was concentrated to ca 100 mL, which was extracted with Et_2O (300 mL). The extract was washed with brine, dried, and evaporated in vacuo to give an oily residue, which was purified by the usual flash column chromatography with benzene to afford diol **16** (22.713 g, 77.5% yield) as a colorless oil: ^1H NMR (100 MHz) δ 1.6–2.4 (6 H, m), 3.2–3.9 (4 H, m), 4.66 (2 H, brs), 5.4–5.7 (2 H, m); IR ($CHCl_3$) 3626, 3387 cm^{-1}; calcd for $C_8H_{14}O_2$ MW 142.0992, found MS, *m/e* 142.0944 (M^+).

Preparation of Ditosylate 18. A solution of *p*-toluenesulfonyl chloride (99.600 g, 0.5238 mol) in pyridine (100 mL) was added to a solution of diol **16** (24.800 g, 0.1746 mol) in pyridine (300 mL). After being stirred at room temperature for 24 h, the reaction mixture was poured into cold water and extracted with benzene. The benzene portion was washed with aqueous diluted HCl solution and with brine, dried, and evaporated in vacuo to give a crude product, which was recrystallized from ether–hexane to afford ditosylate **18** (56.674 g, 72.1% yield) as colorless needles: mp 91.5–92.5 °C; ^1H NMR (100 MHz) δ 1.5–2.5 (6 H, m), 2.46 (6 H, s), 3.92 (4 H, d, *J* = 6.8 Hz), 5.4–5.6 (2 H, m), 7.2–7.8 (8 H, m); IR ($CHCl_3$) 1598 cm^{-1}; MS, *m/e* 449 ($M^+ - 1$). Anal. Calcd for $C_{22}H_{26}O_6S_2$: C, 58.65; H, 5.82. Found: C, 58.77; H, 5.85.

***cis*-4-Cyclohexen-1,2-ylenebis(acetic acid) (4).** 95% NaCN (2.280 g, 44.2 mmol) was added to a solution of **18** (6.622 g, 14.7 mmol) in Me_2SO (30 mL). The mixture was heated at 90 °C with stirring under N_2 for 4 h. The reaction mixture was poured into aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was treated as usual to give an oily residue, which was dissolved in EtOH (25 mL) and a solution of KOH (3 g) in water (6 mL) was added. After being reflued under N_2 for 4 days, the reaction mixture was condensed in vacuo to remove EtOH. The condensed alkaline solution was neutralized with cold aqueous diluted HCl solution and extracted with ether. The ethereal portion was washed with brine, dried, and evaporated in vacuo to give bis(acetic acid) **4** (2.171 g, 74.5% yield from **18**) as an amorphous solid. The structure of **4** was confirmed by its dimethyl ester: colorless oil; ^1H NMR (100 MHz) δ 1.6–2.6 (10 H, m), 3.67 (6 H, s), 5.5–5.7 (2 H, m); IR ($CHCl_3$) 1735 cm^{-1}; calcd for $C_{12}H_{18}O_4$ MW 226.1204, found MS, *m/e* 226.1197 (M^+).

Condensation between *cis*-4-Cyclohexen-1,2-ylenebis(acetic acid) (4) and 4(*R*)-MCTT (5). A mixture of bis(acetic acid) **4** (4.152 g, 21.0 mmol), 4(R)-MCTT (**5**) (7.811 g, 44.1 mmol), DCC (9.968 g, 48.3 mmol), and pyridine (50 mL) was stirred at room temperature under N_2 for 6 days and a large amount of toluene was added. The solvent was evaporated off in vacuo to give an oily residue, which was treated with AcOEt. The precipitate (DC urea) was filtered off and the filtrate was evaporated in vacuo to give an oily residue, which was chromatographed on a silica gel short column with benzene utilizing the usual flash chromatograph apparatus to afford diamide **19** (6.883 g, 63.6% yield) as yellow needles (from AcOEt–hexane): mp 128–128.5 °C; $[\alpha]^{20}_D$ −163.84° (*c* 1.59, $CHCl_3$); ^1H NMR (100 MHz) 1.5–2.7 (6 H, m), 2.8–3.9 (8 H, m), 3.82 (3 H, s), 3.83 (3 H, s), 5.50–5.64 (2 H, m), 5.66 (2 H, dd, *J* = 8 and 2.2 Hz); IR ($CHCl_3$) 1751, 1703 cm^{-1}; MS, *m/e* 516 (M^+). Anal. Calcd for $C_{20}H_{24}N_2O_6S_4$: C, 46.69; H, 4.68; N, 5.42. Found: C, 46.43; H, 4.69; N, 5.41.

Aminolysis of Diamide 19 with Piperidine. A solution of piperidine (183 mg, 2.15 mmol) in THF (5 mL) was added to a solution of **19** (1.110 g, 2.15 mmol) in THF (30 mL) at −78 °C for 3 h. The reaction mixture was evaporated in vacuo to give a yellow oily residue, which was checked by HPLC (JASCO Tri Rotar SR-2): detection, UV (305 nm); column, JASCO Finepak SIL; Solvent system, hexane–AcOEt (3:2); flow volume, 3.7 mL/min; retention time, 13.94 min for **20** and 15.86 min for **21**; ratio, **20**:**21** = 94.0:6.0. The residue was chromatographed by the flash technique on a silica gel short column with benzene–AcOEt (9:1) to give a diastereomeric mixture of **20** and **21** (581 mg, 63.8% yield) as yellow crystals. Recrystallization of the mixture from CH_2Cl_2–hexane afforded a sole pure compound **20** (467 mg, 51.2% yield from **19**) as yellow needles: mp 125–125.5 °C; $[\alpha]^{20}_D$ −130.59° (*c* 2.14, $CHCl_3$); ^1H NMR (100 MHz) δ 1.2–2.6 (14 H, m), 2.96–3.84 (8 H, m), 3.83 (3 H, s), 5.5–5.7 (2 H, m), 5.67 (1 H, dd, *J* = 8.5 and 2.2 Hz); IR ($CHCl_3$) 1755, 1703, 1619 cm^{-1}; MS, *m/e* 424 (M^+). Anal. Calcd for $C_{20}H_{28}N_2O_4S_2$: C, 56.58; H, 6.64; N, 6.60. Found: C, 56.43; H, 6.73; N, 6.63.

***cis*-Cyclohexan-1,2-ylenebis(acetic acid) (23).** A solution of *p*-toluenesulfonyl chloride (39.595 g, 208.5 mmol) in pyridine (100 mL) was added to a solution of diol **15** (10.003 g, 69.5 mmol) in pyridine (100 mL). After being stirred at room temperature for 24 h, the reaction mixture was subjected to the usual workup to give the ditosylate derivative (23.454 g, 74.7% yield) as colorless needles (from ether–hexane): mp 79.5–80 °C; ^1H NMR (100 MHz) δ 1.0–1.6 (8 H, m), 1.8–2.2 (2 H, m), 2.46 (6 H, s), 3.91 (4 H, d,

J = 6.8 Hz), 7.2–7.8 (8 H, m); IR ($CHCl_3$) 1600 cm^{-1}. Anal. Calcd for $C_{22}H_{28}O_6S_2$: C, 58.39; H, 6.23. Found: C, 58.50; H, 6.03.

95% NaCN (4.1 g, 79.5 mmol) was added to a solution of the ditosylate (12 g, 26.5 mmol) in Me_2SO (50 mL) and the mixture was heated at 90 °C with stirring under N_2 for 4 h. The reaction mixture was treated as usual to give the crude dicyanide derivative as an oil. It was dissolved in EtOH (50 mL) and a solution KOH (6 g) in water (12 mL) was added. After being refluxed for 4 days, the reaction mixture was subjected to the usual treatment to afford diacetic acid **23** (3.865 g, 72.8% yield from the ditosylate) as an colorless amorphous solid. The structure was confirmed for its dimethyl ester: colorless oil; ^1H NMR (100 MHz) δ 1.2–1.7 (8 H, m), 2.0–2.4 (6 H, m), 3.67 (6 H, s); IR ($CHCl_3$) 1731 cm^{-1}; calcd for $C_{12}H_{21}O_4$ MW 228.1437, found MS, m/e 229.1426 ($M^+ + 1$).

Condensation between *cis*-4-Cyclohexan-1,2-ylenebis(acetic acid) (23) and 4(*R*)-MCTT (5). A mixture of bis(acetic acid) **23** (4.965 g, 24.8 mmol), 4(*R*)-MCTT (**5**) (9.228 g, 52.1 mmol), DCC (11.253 g, 54.6 mmol), and pyridine (90 mL) was stirred at room temperature under N_2 for 6 days. The reaction mixture was treated as usual to afford diamide **24** (8.980 g, 69.8% yield) as yellow needles (from CH_2Cl_2–hexane): mp 120–120.5 °C; $[\alpha]^{20}_D$ −181.3° (c 1.80, $CHCl_3$); ^1H NMR (100 MHz) 1.0–1.8 (8 H, m), 2.2–2.6 (2 H, m), 2.8–3.9 (8 H, m), 3.82 (3 H, s), 3.83 (3 H, s), 5.65 (1 H, dd, J = 8.3 and 2.2 Hz), 5.66 (1 H, dd, J = 8.3 and 2.2 Hz); IR ($CHCl_3$) 1751, 1740, 1700 cm^{-1}; MS, m/e 518 (M^+). Anal. Calcd for $C_{20}H_{26}N_2O_6S_4$: C, 46.31; H, 5.05; N, 5.40. Found: C, 46.53; H, 5.24; N, 5.25.

Aminolysis of Diamide 24 with Piperidine. A solution of piperidine (458 mg, 5.37 mmol) in THF (5 mL) was added to a solution of diamide **24** (2.784 g, 5.37 mmol) in THF (30 mL) at −78 °C with stirring under N_2. After being stirred at −78 °C for 2 h, the reaction mixture was treated as usual to give a yellow oily residue, which was checked by HPLC according to the same manner as in the case of aminolysis of diamide **19** (retention time for **25**, 14.00 min; for **26**, 17.33 min; ratio, **25**:**26** = 89.3:10.7). The residue was chromatographed on a silica gel column by the usual flash technique with $CHCl_3$–ether (1:1) to give a diastereomeric mixture of **25** and **26**, (1.550 g, 67.7% yield) as yellow amorphous substance, which was subjected to the flash column chromatography with benzene as an elution solvent to afford the major product **25** (877 mg, 38.3% yield from **24**) as yellow needles (from CH_2Cl_2–hexane): mp 124–124.5 °C; $[\alpha]^{20}_D$ −84.18° (c 4.38, $CHCl_3$); ^1H NMR (100 MHz) δ 1.0–2.5 (18 H, m), 2.9–4.0 (8 H, m), 3.81 (3 H, s), 5.65 (1 H, dd, J = 8.5 and 2.0 Hz); MS, m/e 426 (M^+). Anal. Calcd for $C_{20}H_{30}N_2O_4S_2$: C, 56.31; H, 7.09; N, 6.57. Found: C, 56.47; H, 7.18; N, 6.36.

Treatment of Compound 25 with *N*-Benzyl-*N*-methylamine. To a yellow solution of compund **25** (126 mg, 0.30 mmol) in THF (5 mL) was added a solution of *N*-benzyl-*N*-methylamine (39 mg, 0.33 mmol) in THF (1 mL) at room temperature with stirring under N_2. The original yellow color disappeared with 3 min of stirring. The reaction mixture was evaporated in vacuo to give an oily residue, which was purified by preparative TLC (benzene–AcOEt 3:2) to afford diamide **27** (58 mg, 53.2% yield) as a colorless oil: $[\alpha]^{20}_D$ +7.14° (c 2.10, $CHCl_3$); ^1H NMR (100 MHz) δ 1.0–1.9 (14 H, m), 2.93 (3 H, s), 3.0–3.7 (4 H, m), 4.58 (2 H, s), 6.8–7.4 (5 H, m); IR ($CHCl_3$) 1623 cm^{-1}; calcd for $C_{23}H_{34}N_2O_2$ MW 370.2621, found MS, m/e 370.2628 (M^+).

Aminolysis of Compound 20 with *N*-Benzyl-*N*-methylamine. The usual treatment of compound **20** (229 mg, 0.54 mmol) with *N*-benzyl-*N*-methylamine (72 mg, 0.59 mmol) in THF (4 mL) gave diamide **28** (98.5 mg, 50% yield) as a colorless oil: $[\alpha]^{20}_D$ −12.20° (c 4.93, $CHCl_3$); ^1H NMR (100 MHz) δ 1.2–2.7 (16 H, m), 2.93, 2.95 (3 H, each s, a single peak (3 H, s) at δ 2.92 was observed by the determination at 50–60 °C.), 3.2–3.7 (4 H, m), 4.55, 4.59 (2 H, each s, a single peak (2 H, s) at 4.56 was observed by the determination at 50–60 °C.), 5.4–5,7 (2 H, m), 7.0–7.5 (5 H, m); IR ($CHCl_3$) 1625 cm^{-1}; calcd for $C_{23}H_{32}N_2O_2$ MW 368.2461, found MS, m/e 368.2461 (M^+).

Hydrogenation of Diamide 28: 5% Pd on charcoal (20 mg) was added to a solution of **28** (98.5 mg, 2.68 mmol) in EtOH (5 mL) and the mixture was stirred at room temperature under H_2 overnight. The usual treatment of the reaction mixture gave compound **29** (73.5 mg, 74.2% yield) as a colorless oil: $[\alpha]^{20}_D$ −7.13° (c 3.68, $CHCl_3$). Its ^1H NMR, IR, and MS spectra were shown to be completely identical with those of compound **27**.

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Registry No. **1**, 626-51-7; **4**, 25886-62-8; **4** (dimethyl ester), 97920-03-1; **5**, 80963-80-0; **8**, 80963-69-5; **9** (Nu^1 = $PhCH_2NH$), 97919-94-3; **9** (Nu^1 = *N*-pyrrolidinyl), 97919-96-5; **9** (Nu^1 = C6H12N), 97919-98-7; **9** (Nu^1 = morpholino), 97920-00-8; **9** (Nu^1 = NBu_2), 97920-01-9; **9a**, 80963-70-8; **10** (Nu^1 = PhCH2NH), 97919-95-4; **10** (Nu^1 = *N*-pyrrolidinyl), 97919-97-6; **10** (Nu^1 = C6H12N), 97919-99-8; **10** (Nu^1 = morpholino), 97950-36-2; **10** (Nu^1 = NBu2), 97920-02-0; **10a**, 80963-71-9; **11a**, 80963-74-2; **11b**, 80963-75-3; **11c**, 80963-73-1; **11d**, 87476-45-7; **11e**, 87476-44-6; **11f**, 87476-46-8; **11g**, 91793-75-8; **11h**, 91794-26-2; **11i**, 91793-76-9; **11j** (keto form), 80963-77-5; **11j** (enol form), 80963-78-6; **11k**, 87476-47-9; **12c**, 80963-79-7; **13**, 91794-29-5; **14**, 61898-56-4; **15**, 15753-50-1; **15** (ditosylate derivative), 59461-66-4; **15** (dicyanide derivative), 97920-04-2; **16**, 20141-17-7; **17**, 2305-26-2; **18**, 32970-96-0; **19**, 97919-89-6; **20**, 97919-90-9; **21**, 97995-47-6; **23**, 610-09-3; **24**, 97919-91-0; **25**, 97919-92-1; **26**, 97995-48-7; **27**, 97919-93-2; **28**, 97920-05-3; **29**, 97995-49-8; CS2, 75-15-0; H_2O, 7732-18-5; L-cysteine methyl ester hydrochloride, 18598-63-5; *p*-bromobenzenethiol, 106-53-6; 1,1-dimethylethanethiol, 75-66-1; (*R*)-α-methylbenzylamine, 3886-69-9; (*S*)-α-methylbenzylamine, 2627-86-3; *p*-bromoaniline, 106-40-1; β-phenylethyl alcohol, 60-12-8; *epi*-androsterone, 481-29-8; trimethyloxosulfonium chloride, 5034-06-0; ethyl malonate, 105-53-3; benzylamine, 100-46-9; pyrrolidine, 123-75-1; piperidine, 110-89-4; hexahydroazepine, 111-49-9; morpholine, 110-91-8; dibutylamine, 111-92-2.

Supplementary Material Available: Tables of crystal data, atomic positional and thermal parameters, bond lengths, and bond angles, ball and stick representations for compounds **19** and **20**, and 400 MHz ^1H NMR spectra of the methylene region of compounds **19** and **24** (24 pages). Ordering information is given on any current masthead page.