Synthesis of Eudistomins (I). Preparation of (±)-N(10)-Benzyloxycarbonyldebromoeudistomin L.

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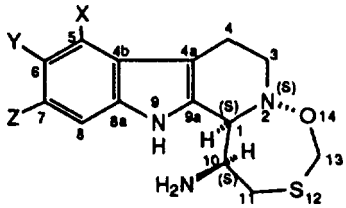
Four plausible precursors (**21**, **22**, **24**, and **25**), just prior to formation of the oxathiazepine ring in eudistomin, were synthesized by the Pictet-Spengler condensation of N-hydroxytryptamine (**15**) or N-hydroxytryptophan ester (**19**) with cysteinal derivatives (**5** and **10**). In the case of the parent compound (**21**), one of these four precursors, treatment with dihalomethane in the presence of a phase transfer catalyst gave an eudistomin analogue (**26**) having the oxathiazepine ring in 35-50% yield.

Introduction

Eudistomins C, E, K, and L were isolated from colonial Caribbean tunicate *Eudistoma olivaceum*, the most active antiviral species in the Alpha Helix Cribbean Expedition 1978.[1] These marine natural products were found to inhibit the growth of *Herpes Simplex* virus, type 1.[2] Their stereochemistry of oxathiazepine ring were defined in 1987 by Blunt and coworkers[3] (Figure 1).

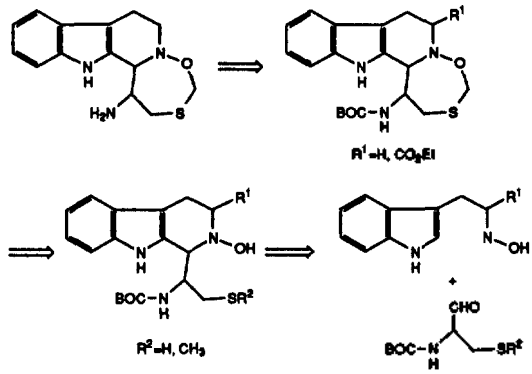
In view of their antiviral properties and their unique ring system which is not found in other natural products, the eudistomins present a challenge of synthetic organic chemists. Several groups have reported preliminary results,[4] most of which were focused on forming oxathiazepine ring. Common in these approaches is the first step, namely the construction of the C-ring by a Pictet-Spengler reaction of a N-hydroxytryptamine derivative and a cysteinal derivative. However, the subsequent ring closure of the oxathiazepine ring appeared to be a difficult task, and only recently two reports concerned with a total synthesis of eudistomin L[5] and N(10)-acetyleudistomin L[6] in very poor yields. Hermkens *et al.* reported the synthesis of (±)-deaminodebromoeudistomin L using an intramolecular Pictet-Spengler reaction of N-alkoxytryptamins.[7]

In the previous studies,[8] it was attempted to form a seven membered oxathiazepine ring by ring expansion of five membered thiazolidine ring, which was not successful. The present study reports our attempt to synthesize eudistomin analogues containing a oxathiazepine ring from compound **21** using bromochloromethane or dibromomethane in the presence of a phase transfer catalyst.



	X	Y	Z
Eudistomin C	H	OH	Br
Eudistomin E	Br	OH	H
Eudistomin K	H	H	Br
Eudistomin L	H	Br	H

Figure 1. Structures of Eudistomin C, E, K and L



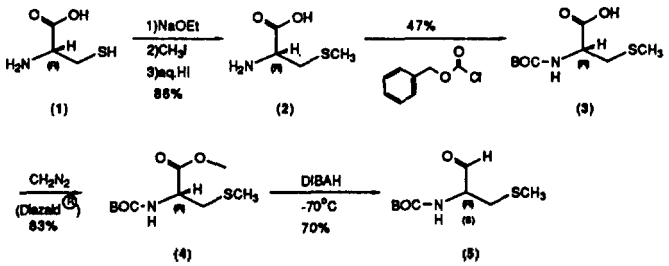
Scheme 1. Retro synthetic plan to Eudistomins C, E, K and L.

Results and Discussion

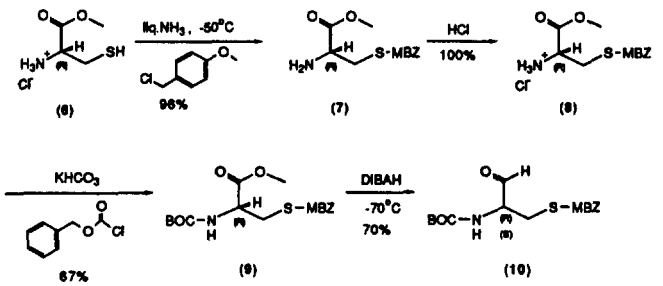
Our retro synthetic plan is shown in Scheme 1.

Accordingly, two derivatives of the cysteinal were prepared. Thus, N-(benzyloxycarbonyl)-S-methylcysteine aldehyde (**5**) was prepared in 24% overall yield from L-cysteine (**1**): S-Methylation of L-cysteine (**1**) was achieved with methyl iodide[9] in 81% yield, and the amino group of S-methyl-L-cysteine (**2**) was protected with a benzyloxycarbonyl (BOC) group[10] in 47% yield. Subsequent esterification of N-(benzyloxycarbonyl)-S-methyl-L-cysteine (**3**)[9] with diazomethane[11] gave N-(benzyloxycarbonyl)-S-methyl-L-cysteine methyl ester (**4**) in 83% yield. Finally, N-(benzyloxycarbonyl)-S-methylcysteine aldehyde (**5**) were obtained in 70% yield by reduction of methyl ester (**4**) with diisobutylaluminium hydride (DIBAH)[12] (Scheme 2).

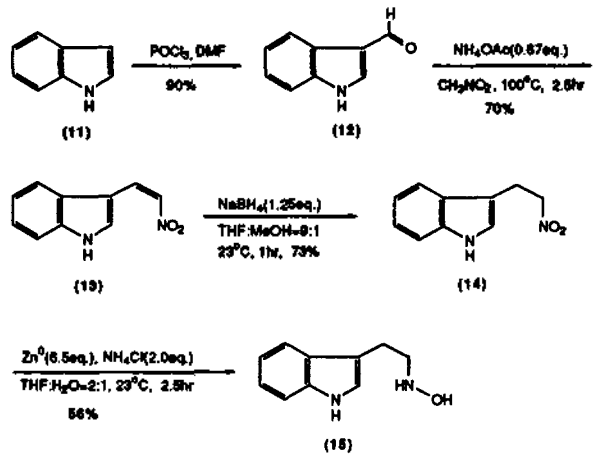
S-(p-Methoxybenzyl)-N-(benzyloxycarbonyl) cysteine aldehyde (**10**) was also prepared in 45% overall yield from L-crystine methyl ester hydrochloride (**6**): The thiol group of L-cysteine methyl ester hydrochloride (**6**) was protected with p-methoxybenzyl (MBZ) group[13] in 96% yield, and then the amino group of resulting S-(p-methoxybenzyl)-L-cysteine methyl ester (**7**) was again protected with BOC group[12a] in 67% yield, and then selectively reduced with DIBAH[12] to give N,S-protected cysteine aldehyde (**10**) in 70% yield (Scheme 3).



Scheme 2. Synthesis of N-(benzyloxycarbonyl)-S-methylcysteine aldehyde (**5**).



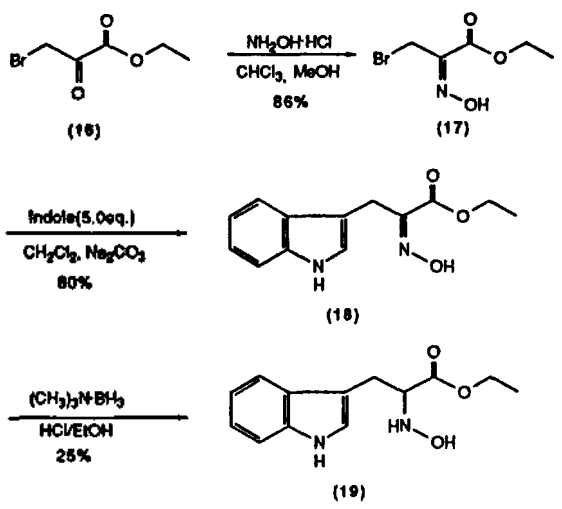
Scheme 3. Synthesis of S-(*p*-methoxybenzyl)-N-(benzyloxycarbonyl) cysteine aldehyde (**10**).



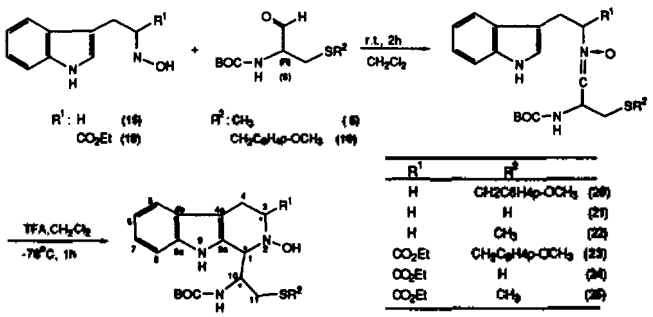
Scheme 4. Synthesis of N-hydroxytryptamine (**15**).

Next, N-hydroxytryptamine (**15**) was prepared in 26% overall yield from indole (**11**): Vilsmeier-Haak reaction of indole (**11**) with dimethylformamide, phosphorus oxychloride [14] gave 3-formylindole (**12**) in 90% yield. Subsequently, 3-(β-Nitro)vinylindole (**13**) was then prepared in 70% yield by the reaction of 3-formylindole (**12**) with nitromethane.[15] By reducing the compound (**13**) with sodium borohydride.[16] 3-(β-nitro) ethylindole (**14**) was obtained in 73% yield. In the last step, the reduction of (**14**) with zinc powder[17] gave N-hydroxytrytryptamine (**15**) in 56% yield (Scheme 4).

Ethyl α-hydroxyamine-β-(indol-3-yl) propanoate (**19**) was also prepared in 17% overall yield by using ethyl bromopyruvate (**16**) as a starting material, which was treated with hydroxylamine hydrochloride,[18] to give the bromooxime (**17**) in 86% yield. Subsequent alkylation of indole with the bromide (**17**) provided ethyl α-(hydroxyimino)-β-(indol-3-yl)-propanoate (**18**)[19] in 80% yield. Reduction of indole oxime (**18**)



Scheme 5. Synthesis of α-(hydroxyamino)-β-(indole-3-yl)propanoate (**19**).



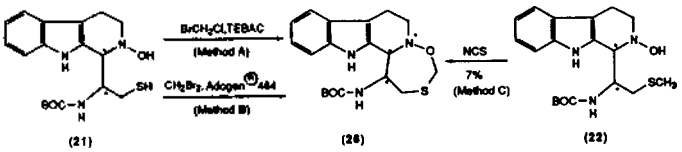
Scheme 6. Pictet-spengler reaction of cysteinal part (**5** and **10**) with tryptamine part (**15** and **19**).

with trimethylamine-borane complex[20] gave ethyl α-(hydroxyamino)-β-(indol-3-yl)propanoate (**19**) in 25% yield (Scheme 5).

Pictet-Spengler (PS) condensations of cysteinal part (compound **5** and **10**) with tryptamine part (compound **15** and **19**) were performed in the presence of trifluoroacetic acid (TFA). When the aldehyde part (**5**, **10**) and compound (**15**) or (**19**) of the tryptamine part was stirred at room temperature under nitrogen, the corresponding nitrone was obtained. And, when the nitrone were treated with TFA at −78℃ *in situ*, the corresponding 2-hydroxyl-1,2,3,4-tetrahydro-β-carboline derivatives (**20**, **22**, **23**, and **25**) were obtained (Scheme 6).

PS reaction of tryptamine (**15**) with cysteinal (**10**) yielded PS reaction product (**20**). The product (**20**) was a mixture of diastereomers, (1S, 10S)(1R, 10R) and (1S, 10R)(1R, 10S), with high diastereoselectivity (7 : 1) for (1S, 10S)(1R, 10R). Enantiomeric mixtures (1S, 10S) and (1R, 10R) (**20**) were separated by recrystallization in 40% yeild. The S-protecting group had to be removed as mildly as possible. When *p*-methoxybenzyl group of (1S, 10S) and (1R, 10R) (**20**) was removed by reacting with freshly prepared mercuric trifluoroacetate,[5c] plausible precursors (1S, 10S) and (1R, 10R) (**21**) were obtained in 30% yield.

PS reaction of tryptamine (**15**) with cysteinal (**5**) yielded compound (**22**). The compound (**22**) was also a mixture of



Scheme 7. Oxathiazepine ring formation from (**21**), (**22**).

diastereomers (1S, 10S) (1R, 10R) and (1S, 10R) (1R, 10S) with high diastereoselectivity (5 : 1) for (1S, 10S)(1R, 10R). The mixture of enantiomers, (1S, 10S) and (1R, 10R), were separated by low pressure preparative LC, and plausible precursors (1S, 10S) and (1R, 10R) (**22**) were obtained in 64% yield.

PS reaction of N-hydroxytryptamine (**19**) with cysteinal (**10**) yielded compound (**23**) as a mixture of diastereomers. These diastereomers were composed of (1S, 3R, 10S), (1R, 3R, 10R), (1R, 3R, 10S), and (1S, 3R, 10R) in the same ratio. The diastereomer (1S, 3R, 10S) (**23**) was obtained in 18% yield by the column chlomatographic separation. Treatment of (1S, 3R, 10S) (**23**) with mercuric trifluoroacetate gave a compound (1S, 3R, 10S) (**24**), a possible precursor of eudistomin L, in 41% yield.

Similarly, PS reaction of N-hydroxytryptamine (**19**) with crysteinal (**5**) yielded compound (**25**), a mixture of diastereomers. These diastereomers was (1S, 3R, 10S), (1R, 3R, 10R), (1R, 3R, 10S), and (1S, 3R, 10R) in the same ratio. Column chromatographic separation gave a plausible precursor (1S, 3R, 10S) (**25**) in 18% yield. In the way, four plausible precursors (**21**, **22**, **45**, and **25**) were synthesized.

The phase transfer alkylation of (1S, 10S) and (1R, 10R) (**21**) was carried out with bromochloromethane and triethylbenzylammonium chloride (TEBAC)[7a] in 50% yield (method A). Another oxathiazepine ring formation of (1S, 10S) and (1R, 10R) (**21**) was reacted with dibromomethane and Adogen 464[21] in 35% yield (method B). Then, (±)−*N*(10)-benzyloxycarbonyl-debromoeudistomin L (**26**) were obtained from (1S, 10S) and (1R, 10R) (**21**) using dihalomethane and PTC in 35-50% yield (Scheme 7).

The compound (1S, 10S) and (1R, 10R) (**26**) was also prepared by treating (1S, 10S) and (1R, 10R) (**22**) with N-chlorosuccinimide (NCS) by the procedure of Nakagawa *et al.*[5] in 7% isolated yield (method C). In a ^{1}H-NMR spectrum, a peak for the thiomethyl group disappeared at 2.1 ppm, and a new peak appeared at 4.2 ppm, suggesting that the oxathiazepine ring was formed and this new peak stood for the methylene group between sulfur atom and oxygen atom. Also, in a ^{13}C-NMR spectrum, the deshielding of the peak for the thiomethyl group from 15 ppm to 75 ppm further supports the explanation that the ring formation has occurred.

In conclusion, we have synthesized the eudistomin analogue (1S, 10S) and (1R, 10R) (**26**) from (1S, 10S) and (1R, 10R) (**21**) using dihalomethane and PTC. Further efforts for the formation of the oxathiazepine ring system in (1S, 3R, 10S) (**24**) and (1S, 3R, 10S) (**25**) as well as the removal of the ethoxycarbonyl group are currently under investigation in our laboratories.

Experimental

All the reactions were followed using a HPLC equipped with a μ-Bondapak C_{18} column and a UV detector. Melting points were taken on a Buchi 535 melting point apparatus, and were not corrected. The structures of synthetic compounds were identified by using the ^{1}H-NMR and ^{13}C-NMR spectra measured on a Bruker AM-300 spectrometer with TMS as an internal standard. The infrared spectra were recorded with an Analect FT-IR fx-6160 Spectrophotometer. Optical rotations were measured by a JASCO DIP-360 Digital Polarimeter.

Purification and isolation of synthetic compounds were progressed with a low pressure preparative liquid chromatography with a Silicagel 60 (70-230 mesh ASTM) column and a 254 nm UV Prep-detector, or a preparative HPLC system with a JAI LC-908 recycle liquid chromatograph equipment.

S-Methyl-L-cysteine (2). L-Cysteine (**1**) (29.1 g, 0.24 mole) was suspended in absolute alchol (350 m*l*), and freshly cut pieces of sodium (14.7 g, 0.64 mole) were then added (in a 15 min interval) to the above solution. After all the sodium was dissolved, methyl iodide (16.6 m*l*, 0.26 mole) was added and the mixture was stirred at room temperature for 15 min. The solution was acidified by adding 48% aqueous hydroiodic acid to pH 4, and large quantities of white solid were formed. The white solid were collected by filtration, washed with cold absolute ethanol, and dried to give S-methyl-L-cysteine (**2**) (28 g, 0.21 mole, 86%), mp. 222-225℃ (lit.[9] 241-245℃); $[\alpha]_D^{25}$ −18.0° (c 1.0, H_2O) (lit.[22] −32.3°); IR (KBr) 3500, 1640, 1500, 1430, 1360, 1300, 1200 cm^{-1}; ^{1}H-NMR (D_2O) δ 3.8 (m, 1H), 2.8 (m, 2H), 2.0 (s, 3H); ^{13}C-NMR (D_2O) δ 176.0, 56.0, 37.1, 17.3.

N-(Benzyloxycarbonyl)-S-methyl-L-cysteine (3). To a solution of S-Methyl-L-cysteine (**2**) (27 g, 0.2 mole) in 2N aqueous sodium hydroxide solution (400 m*l*) at 0℃ was added benzyl chloroformate (35.83 g, 0.21 mole). The resulting mixture was vigorously stirred at 25℃ for 3-4 h, maintaining the pH of the mixture was maintained at 13.3. The mixture was basified (pH 14) by addition of 2 N aqueous sodium hydroxide (500 m*l*). Impurity was then extracted with ethyl acetate, and aqueous layer was acidified using 35% hydrochloric acid to pH 1. It was then extracted with ethyl acetate. The organic extracts were washed with brine solution, and dried over magnesium sulfate, filtered, and evaporated to give N-(benzylloxycarbonyl)-S-methyl-L-cysteine (**3**) (25.3 g, 0.094 mole, 47%) as an oil. $[\alpha]_D^{20}$ −24.5° (c 1.0, MeOH); IR ($CHCl_3$) 3480, 3000, 1740, 1520, 1080 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 10.5 (s, 1H), 7.3 (m, 5H), 5.7 (d, 1H), 5.1 (s, 2H), 4.6 (m, 1H), 3.0 (m, 2H), 2.1 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 176.0, 156.7, 136.6, 129.2, 129.0, 128.9, 128.8, 128.7, 68.0, 53.9, 37.0, 16.9.

N-(Benzyloxycarbonyl)-S-methyl-L-cysteine Methylester (4). To a solution of N-(benzyloxycarbonyl)-S-methyl-L-cysteine (**3**) (20.6 g, 76.5 mmole) in anhydrous 1 *l* of diethyl ether was added a solution of diazomethane, formed by reacting alcoholic potassium hydroxide with Diazald (N-methyl-N-nitroso-p-toluenesulfonamide), in diethyl ether and alcohol. When a light green color persisted in the reaction mixture, the addition of diazomethane was stopped and the stirring was continued for another 1 h. After filtration, the reaction mixture was concentrated *in vacuo* to give N-(benzyloxycarbonyl)-S-methyl-L-cysteine methyl ester (**4**) (17.95 g, 63.4 mmol, 83%). mp. 61-62℃; $[\alpha]_D^{20}$ −36.6° (c 1.0, MeOH); IR ($CHCl_3$) 3400, 1720, 1220 cm^{-1}; ^{1}H-NMR ($CDCl_3$)

δ 7.2 (m, 5H), 5.7 (d, 1H), 5.0 (d, 2H), 4.5 (q, 1H), 3.6 (s, 3H), 2.8 (m, 2H), 2.0 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.0, 156.4, 136.8, 129.1, 128.8, 128.7, 67.7, 54.0, 53.2, 37.2, 16.7.

N-(Benzyloxycarbonyl)-S-methylcysteine Aldehyde (5). To a cooled (−76℃) and stirred solution of N-(benzyloxycarbonyl)-S-methyl-L-cysteine methyl ester (**4**) (14.2 g, 50 mmole) in dry toluene (600 m*l*) was added dropwise diisobutylaluminum hydride (111 m*l*, 1 M solution in n-hexane, Aldrich Chem. Co.) over a period of 1 h in a nitrogen atmosphere. After the mixture was stirred for another 2 h at −76 ℃, the excess of the reagent was decomposed by carefully adding of mixture of ethanol/concentrated aqueous HCl (58.4 m*l*, 10/1, v/v) to it. Then 760 m*l* of water was added, and the organic layr was separated. The aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and evaporated to give an oil (12.6 g). Flash column chromatography (hexane/ethyl acetate, 5/2, v/v) gave N-(benzyloxycarbonyl)-S-methyl cysteine aldehyde (**5**) (8.86 g, 35 mmole, 70%), $[\alpha]_D^{20}$ −1.0° (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 9.7 (s, 1H), 7.3 (m, 5H), 5.7 (s, 1H), 5.1 (m, 2H), 4.4 (m, 1H), 3.0 (m, 2H), 2.1 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 199.0, 156.4, 136.8, 129.2, 129.1, 128.9, 128.8, 67.9, 59.9, 34.3, 17.1.

S-(*p*-Methoxybenzyl)-L-cysteine Methyl Ester (7). *p*-Methoxybenzyl chloride (15.7 g, 0.1 mole) was added dropwise with stirring to a solution of L-cysteine methyl ester hydrochloride (**6**) (17.2 g, 0.1 mole) in liquid ammonia (200 m*l*) in a flask protected from atmospheric moisture, the temperature being kept at −60℃. The resulting mixture was vigorously stirred at −50℃ for 5 h in a nitrogen atmosphre. The reaction mixture was concentrated *in vacuo*, and extracted with 500 m*l* of methylene chloride. The organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to give S-(*p*-methoxybenzyl)-L-cysteine methyl ester (7) (24.5 g, 0.096 mole, 96%), mp. 15-20℃; $[\alpha]_D^{20}$ −26.0° (c 1.0, MeOH); ^{1}H-NMR (DMSO-d_6) δ 7.2 (d, 2H), 6.9 (d, 2H), 3.7 (s, 3H), 3.7 (s, 2H), 3.6 (s, 3H), 3.5 (t, 1H), 2.8 (s, 2H), 2.6 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ 175.0, 158.1, 130.5, 130.1, 130.0, 129.9, 113.7, 55.0, 54.0, 51.5, 35.5, 34.9.

S-(*p*-Methoxybenzyl)-L-cysteine Methyl Ester hydrochloride (8). To a S-(*p*-methoxybenzyl)-L-cysteine methyl ester (**7**) (24.0 g, 94 mmole) was added 35% hydrochloric acid (98.0 g, 0.94 mole). Vacuum evaporation of the solution gave S-(*p*-methoxybenzyl)-L-cysteine methyl ester hydrochloride (**8**) (27.4 g, 94 mmole, 100%), mp. 135-140℃; $[\alpha]_D^{20}$ −12.8° (c 1.0, MeOH); ^{1}H-NMR (DMSO-d_6) δ 8.9 (s, 3H), 7.3 (d, 2H), 6.9 (d, 2H), 4.3 (t, 1H), 3.8 (s, 2H), 3.7 (s, 3H), 3.7 (s, 3H), 3.0 (d, 2H); ^{13}C-NMR (DMSO-d_6) δ 168.6, 158.3, 130.1, 129.3, 113.8, 55.0, 53.0, 51.7, 34.8, 30.6.

S-(*p*-Methoxybenzyl)-N-(benzyloxycarbonyl)-L-cysteine Methyl Ester (9). To an ice-cooled suspension of S-(*p*-methoxybenzyl)-L-cysteine methyl ester hydrochloride (**8**) (24.7 g, 85 mmole), and sodium bicarbonate (35.7 g, 425 mmole) in H_2O (330 m*l*) and ethyl acetate (500 m*l*), benzyl chloroformate (175 g, 103 mmole) was added with vigorous stirring over a period of 30 min. After stirring for 1 h, the aqueous layer was acidified with 1 N hydrochloric acid (300 m*l*). The organic layer was separated, washed with water, dried over magnesium sulfate and evaporated *in vacuo* to give a crystalline mass. Recrystallization from diethyl ether gave white crystalline S-(*p*-methoxybenzyl)-N-(benzyloxycarbonyl)-L-cysteine methyl ester (**9**) (22.2 g, 57 mmole, 67%), mp. 65-68℃; $[\alpha]_D^{20}$ 60.6° (c 1.0, MeOH); ^{1}H-NMR (DMSO-d_6) δ 7.9 (d, 1H), 7.3 (m, 5H), 7.2 (d, 2H), 6.9 (d, 2H), 5.1 (s, 2H), 4.2 (m, 1H), 3.7 (s, 3H), 3.7 (s, 2H), 3.6 (s, 3H), 2.7 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ 171.3, 166.5, 158.1, 155.9, 130.0, 129.9, 129.7, 128.3, 128.2, 127.8, 127.7, 113.7, 113.6, 65.5, 54.9, 53.6, 52.0, 34.5, 31.9.

S-(*p*-Methoxybenzyl)-N-(benzyloxycarbonyl) Cysteine Aldehyde (10). To a cooled (−76℃) and stirred solution of S-(*p*-methoxybenzyl)-N-(benzyloxycarbonyl)-L-cysteine methyl ester (**9**) (19.5 g, 50 mmole) in dry toluene (600 m*l*) was added dropwise DIBAH (111 m*l*, 1 M solution in *n*-hexane, Aldrich Chem Co.) over a period of 1 h in a nitrogen atmosphere. After the mixture was stirred for another 2 h at −76℃, the excess of the reagent was decomposed by carefully adding the mixture of ethanol/35% HCl (59.4 m*l*, 10/1, v/v) to it. Then 760 m*l* of water was added, and the organic layer was separated. The aqueous layer was washed with ethyl acetate. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered and evaporated to given an oil (17.9g). Flash column chloromatography (hexane/ethyl acetate, 5/2, v/v) gave S-(*p*-methoxybenzyl)-N-(benzyloxycarbonyl) cysteine aldehyde (**10**) (12.5 g 35 mmole, 70%). $[\delta]_D^{20}$ −1.0° (c 1.0, MeOH); ^{1}H-NMR ($CDCl_3$) δ 9.6 (s, 1H), 7.4 (m, 5H), 7.2 (d, 2H), 6.9 (d, 2H), 5.6 (s, 1H), 5.1 (s, 2H), 4.4 (m, 1H), 3.8 (s, 3H), 3.7 (s, 2H), 2.9 (d, 2H), ^{13}C-NMR ($CDCl_3$) δ 198.9, 166.5, 159.5, 155.9, 130.7, 129.2, 129.0, 128.8, 114.7, 114.6, 67.9, 60.0, 55.9, 37.0, 31.1.

3-Formylindole (12). Phosphorus oxychloride (50 m*l*, 0.55 mole) was added dropwise with stirring to dimethylformamide (160 g, 2.2 mole) in a flask protected from atmospheric moisture, the temperature being kept at 10-20℃. Indole (**11**) (58.5 g, 0.5 mole) in dimethylformamide (40 g) was then slowly added with stirring, the temperature of the mixture being kept at 20-30℃. The mixture was kept at 35℃ for 45 min, then poured on crushed ice, and the clear solution treated at 20-30℃ with sodium hydroxide (95 g, 2.4 mole) in 500 m*l* of water, at such a rate that the solution was always acidic, until about three quarters of the alkali had been added. The last quarter was added all at once, and the solution quickly boiled for 1 min. The white crystals were filtered off, carefully washed five times with 250 m*l* of water, and dried to a constant weight at 100℃, 5 mmHg. The off white product, 3-formylindole (**12**) (65.0 g, 0.45 mole, 90%) was obtained. mp. 198-199℃ (lit.[23] 197-199℃); ^{1}H-NMR (DMSO-d_6) δ 12.1 (s, 1H), 10.0 (s, 1H), 8.3 (s, 1H), 8.1 (d, 1H), 7.5 (d, 1H), 7.3-7.2 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ 184.9, 138.4, 137.0, 124.0, 122.1, 120.7, 118.1, 112.3.

3-(β-Nitro)vinylindole (13). A mixture of 3-formylindole (**12**) (58.1 g, 0.4 mole), ammonium acetate (13.4 g, 0.27 mole) and nitromethane (450 m*l*) was refluxed with stirring for 2.5 h. After cooling, reddish brown solid was collected on a filter and crystallization of this product from absolute methanol gave 3-(β-nitro)vinylindole (**13**) (53.0 g, 0.28 mole, 70%). mp. 171-172℃ (lit.[15b] 167-168℃); ^{1}H-NMR (DMSO-d_6) δ 12.2 (s, 1H), 8.4 (d, 1H), 8.2 (d, 1H), 8.0 (s, 1H), 7.9 (m, 1H), 7.5 (d, 1H), 7.3-7.2 (m, 2H); ^{13}C-NMR (DMSO-d_6) δ 137.6, 136.3, 134.7, 131.0, 124.5, 123.3, 121.9, 120.4, 112.7, 108.2.

3-(β-Nitro)ethylindole (14). 3-(β-Nitro)vinylindole

(13) (37.8 g, 0.2 mole) was weighed in a Erlenmeyer flask containing a magnetic stirring bar, and then 1L of mixed solvent system of tetrahydrofuran/methanol (10/1, v/v) was added at room temperature. Sodium borohydride (9.5 g, 0.25 mole) was then added, in ten portions, to the well stirred solution. A mildly exothermic reaction ensued with the gradual disappearance of the yellow coloration. The reaction mixture was stirred for 1 h at room temperature and then quenched with 2 *l* of water. The volatile solvent was removed on a rotary evaporator and the turbid aqueous layer was extracted with 2 *l* of diethyl ether. The combined ether layers were washed with water and brine, dried over magnesium sulfate and the solvent removed under reduced pressure. Nearly pure product was obtained which could be purified by passing it through a short column of silicagel (hexane/ethyl acetate, 5/1, v/v, eluant) to yield 3-(β-nitro)ethylindole (**14**) (27.9 g, 0.146 mole, 73%). mp. 51-52℃; ^{1}H-NMR ($CDCl_3$) δ 8.0 (s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 7.2-7.1 (m, 2H), 7.0 (s, 1H), 4.6 (t, 3H), 3.5 (t, 3H); ^{13}C-NMR ($CDCl_3$) δ 127.2, 123.2, 123.1, 120.5, 118.8, 112.1, 110.6, 76.4, 24.2.

N-Hydroxytryptamine (15). In a flask were placed 3-(β-nitro) ethylindole (**14**) (19.1 g, 0.1 mole), tetrahydrofuran (200 m*l*), water (80 m*l*) and ammonium chloride (10.7 g, 0.2 mole). The mixture was stirred vigorously by means of a mechanical stirrer, and zinc powder of 85% purity (38.5 g, 0.5 mole) was added during the course of 1-2 h at 30-35℃. The tetrahydrofuran were removed on a rotary evaporator and the turbid aqueous layer was extracted with diethytl ether. The ether layers were washed with water, dried over magnesium sulfte and the solvent removed under reduced pressure. Crystallization of this product from chloroform gave N-hydroxytryptamine (**15**) (9.9 g, 0.056 mole, 56%), mp. 108-110℃; ^{1}H-NMR (DMSO-d_6) δ 10.7 (s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 7.2 (s, 1H), 7.1 (s, 1H), 7.0 (t, 1H), 6.9 (t, 1H), 5.6 (s, 1H), 3.0 (t, 2H), 2.8 (t, 2H); ^{13}C-NMR (DMSO-d_6) δ 136.1, 127.2, 122.4, 120.7, 118.2, 118.0, 112.3, 111.2, 54.3, 22.8.

Ethyl α-(hydroxyimino)-β-bromopropanoate (17). Hydroxylamine hydrochloride (3.48 g, 50 mmole) was added to a stirred solution of ethyl bromopyruvate (**16**) (9.75 g, 50 mmole) in chloroform (150 m*l*) and methanol (100 m*l*) at room temperature for 16 h and concentrated to dryness. The residue was dissolved in dichloromethane, washed with 0.1 N HCl and with brine, and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave crystalline ethyl α-(hydroxyimino)-β-bromopropanoate (**17**) (9.03 g, 43 mmole, 86%), which was recrystallized from dichloromethane, *n*-hexane. mp. 78-79℃ (lit.[18b] 76-78℃); ^{1}H-NMR ($CDCl_3$) δ 10.0 (s, 1H), 4.4 (q, 2H), 4.3 (s, 2H), 1.4 (t, 3H); ^{13}C-NMR (CDCl3) δ 161.6, 147.8, 62.5, 30.1, 15.0.

Ethyl α-(hydroxyimino)-β-(indol-3-yl)propanoate (18). A solution of ethyl α-(hydroxyimino)-β-bromopropanoate (**17**) (8.4 g, 40 mmole) in dichloromethane (100 m*l*) was added dropwise to a stirred solution of indole (24.0 g, 200 mmole) and a suspension of sodium carbonate (24.0 g, 220 mmole) in dichloromethane (100 m*l*) at room temperature under nitrogen. Stirring was continued at room temperature for 24 h under nitrogen atmosphere. The mixture was then filtered through celite and concentrated to dryness. The residue was subjected to column chromatography (chloroform/hexane, 1/1, v/v, eluant) to yield crystlline ethyl α-(hydroxyimino)-β-(indol-3-yl)propanoate (**18**) (7.9 g, 32 mmole, 80%), mp. 156-157℃ (lit.[19] 155-157℃); ^{1}H-NMR (DMSO-d_6) δ 12.4 (s, 1H), 10.9 (s, 1H), 7.6 (d, 1H), 7.3 (d, 1H), 7.1 (s, 1H), 7.0 (m, 2H), 4.2 (q, 2H), 3.9 (s, 2H), 1.2 (t, 3H); ^{13}C-NMR (DMSO-d_6) δ 163.7, 150.1, 135.8, 126.8, 123.7, 120.9, 118.5, 118.3, 111.3, 108.3, 60.7, 19.9, 13.9.

Ethyl α-(hydroxyamino)-β-(indol-3-yl)propanoate (19). A solution of hydrochloric acid in ethanol (60 m*l* of a 7 N solution) was added dropwise to a stirred solution of ethyl α-(hydroxyimino)-β-(indol-3-yl)propanoate (**18**) (7.4 g, 30 mmole) and Borane-trimethylamine complex (2.4 g, 33 mmole) in ethanol (150 m*l*) at room temperature under nitrogen atmosphere. Stirring was continued for 5 h. The mixture was then concentrated to dryness, the residue was dissolved in dichloromethane, the solution was neutralized with sodium bicarbonate and filtered. The resulting solution was washed with 0.1 N hydrochloric acid and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* gave crystalline meterial. Recrystallization from dichloromethane, *n*-hexane gave ethyl α-(hydroxyamino)-β-(indol-3-yl)propanoate (**19**) (1.9 g, 7.5 mmol, 25%). mp. 118-119℃; ^{1}H-NMR (DMSO-d_6) δ 10.9 (s, 1H), 7.6 (s, 1H), 7.5 (d, 1H), 7.3 (d, 1H), 7.1 (s, 1H), 7.1 (t, 1H), 7.0 (t, 1H), 5.7 (s, 1H), 4.0 (q, 2H), 3.7 (t, 1H), 2.9 (d, 2H), 1.0 (t, 3H); ^{13}C-NMR (DMSO-d_6) δ 163.6, 136.0, 127.1, 123.5, 120.8, 118.2, 118.1, 111.2, 109.5, 66.4, 59.7, 24.8, 13.9.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-((4-methoxybenzyl)thio)ethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (20). A solution of s-(*p*-methoxybenzyl)-N-(benzyloxycarbonyl)cysteine aldehyde (**10**) (3.95 g, 11 mmole) and N-hydroxytryptamine (**15**) (1.76 g, 10 mmole) in dry dichloromethane (225 m*l*) was stirred for 2 h at room temperature under nitrogen atmosphere. The mixture was cooled to −78 ℃ in dryice-acetone bath, and trifluoroacetic acid (3.0 g, 26.5 mmole) was then slowly added with stirring during the course of 1-2 h at −78℃ under nitrogen atmosphere. After 1 h, the resulting solution was washed with water, dried over magnesium sulfate, filtered, and concentrated to dryness to give a yellow oil. Recrystallization from dichloromethane (50 m*l*) to give white crystalline (1S, 10S) and (1R, 10R) mixture of (**20**) (2.0 g, 3.9 mmole, 39%). mp. 147-149℃; ^{1}H-NMR ($CDCl_3$) δ 7.5 (d, 1H), 7.4-7.0 (m, 12H), 6.8 (d, 2H), 5.6 (s, 1H), 5.1 (d, 2H), 4.8 (s, 1H), 4.3 (s, 1H), 3.9 (s, 2H), 3.8 (s, 3H), 3.1 (m, 4H), 2.9 (s, 2H); ^{13}C-NMR ($CDCl_3$) δ 164.7, 159.0, 136.7, 135.0, 131.7, 130.0, 129.6, 129.4, 128.5, 128.4, 128.2, 128.2, 123.4, 120.4, 120.3, 118.5, 118.3, 114.6, 114.3, 111.6, 107.8, 67.8, 62.3, 55.3, 51.9, 36.4, 35.1, 30.1, 17.2.

1-[1-(Benzyloxycarbonyl)amino-2-mercaptoethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (21). To a stirred solution of (**20**) (0.62 g, 1.2 mmole) in a mixture of acetic acid in 80% aqueous ethanol (5/9, v/v, 28 m*l*) were added freshly prepared mercuric trifluoroacetate (1.0 g, 2.3 mmole) and anisole (0.2 g, 1.85 mmole) as a scavenger. After 24 h, 100 m*l* of water was added. Then hydrogen sulfide was bubbled through this solution for 1 h. The resulting mercuric sulfide was filtered off and was washed several times with ethanol. The volatile solvents were removed on a rotary evaporator and the product was extracted with ethyl acetate. The ethyl acetate layers were washed with water, dried over magnesium sulfate and the solvent removed under reduced pressure. Recrystallization gave (1S, 10S) and (1R, 10R) mixture of (**21**) (0.12 g, 0.3 mmole, 30%), mp. 163-

165℃; ^{1}H-NMR (DMSO-d_6) δ 12.3 (s, 1H), 10.3 (s, 1H), 7.8 (d, 1H), 7.6 (d, 1H), 7.6-7.3 (m, 7H), 7.2 (t, 1H), 5.3 (s, 2H), 4.9 (t, 2H), 4.2 (s, 4H), 3.6 (t, 2H), 2.5 (s, 1H); ^{13}C-NMR (DMSO-d_6) δ 164.7, 135.6, 130.2, 129.1, 128.5, 128.5, 128.4, 128.4, 126.7, 126.7, 123.9, 121.2, 120.7, 117.3, 113.0, 67.5, 58.1, 49.8, 40.3, 19.5, 18.3.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-methylthioethyl]-2-hydroxy-1,2,3,4-tetrahydro-β-carbolines (22). Product (**22**) was prepared from tryptamine (**15**) (1.76 g, 10 mmol) and aldehyde (**5**) (2.8 g, 11 mmole) as described for the preparation of (**20**). Column chromatographic separation (silicagel, hexane/ethyl acetate, 5/2, v/v, eluant) gave (1S, 10S) and (1R, 10R) mixture of (**22**) (2.0 g, 6.4 mmole, 64%). mp. 73-75℃; ^{1}H-NMR ($CDCl_3$) δ 8.9 (s, 1H), 7.5 (d, 1H), 7.4-7.0 (m, 9H), 5.9 (s, 1H), 5.1 (s, 2H), 4.8 (s, 1H), 4.6 (s, 1H), 3.7 (t, 2H), 3.1 (s, 2H), 3.0 (t, 2H) 2.1 (s, 3H); ^{13}C-NMR ($CDCl_3$) δ 157.0, 136.8, 135.8, 128.6, 128.5, 128.4, 128.3, 128.2, 127.1, 122.8, 120.0, 118.3, 111.6, 111.5, 67.4, 65.2, 60.0, 54.2, 36.9, 18.0, 15.9.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-((4-methoxybenzyl)thio)ethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahdro-β-carbolines (23). Product (**23**) was prepared from tryptamine (**19**) (0.25 g, 1.0 mole) and aldehyde (**10**) (0.395 g, 1.1 mmole) as described for the preparation of (**20**). Column chromatographic separation (silicagel, hexane/ethyl acetate, 5/1, v/v eluent) gave (1S, 3R, 10S) (**23**) (0.11 g, 0.18 mole, 18%), mp. 128-129℃; ^{1}H-NMR ($CDCl_3$) δ 7.4-6.6 (m, 14H), 6.5 (m, 1H), 5.4 (s, 1H), 5.1 (s, 2H), 5.0 (d, 1H), 4.2 (q, 2H), 3.9 (m, 1H), 3.8 (t, 1H), 3.7 (s, 2H), 3.7 (s, 3H), 3.4 (d, 2H), 2.7 (d, 2H) 1.3 (t, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.5, 158.7, 155.1, 148.1, 136.5, 130.2, 130.0, 129.1, 129.0, 128.7, 128.6, 128.3, 128.2, 127.9, 123.3, 122.0, 119.6, 114.3, 113.9, 113.7, 111.1, 109.4, 84.1, 69.3, 67.3, 61.4, 55.3, 39.5, 35.6, 33.6, 32.7, 14.1.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-mercaptoethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (24). Product (**24**) was prepared from (1S, 3R, 10S) (**23**) (0.1 g, 0.17 mmole) by treatment with mercuric trifluoroacetate (0.14 g, 0.32 mmole) as described for the preparation of (**21**). Recrystallization gave (1S, 3R, 10S) (**24**) (0.04 g, 0.07 mmole, 41%), mp. 97-99℃; ^{1}H-NMR ($CDCl_3$) δ 8.3 (s, 1H), 7.5-7.0 (m, 9H), 6.4 (s, 1H), 5.6 (d, 1H), 5.0 (d, 1H), 4.9 (s, 2H), 4.3-3.9 (m, 2H), 4.1 (q, 2H), 3.3-2.6 (m, 4H), 1.6 (t, 1H), 1.2 (t, 3H); ^{13}C-NMR ($CDCl_3$) δ 173.4, 157.9, 148.1, 136.2, 132.1, 129.1, 128.8, 128.8, 128.6, 128.3, 122.2, 121.6, 119.8, 118.1, 112.3, 109.8, 85.0, 69.8, 67.1, 35.0, 33.1, 32.2, 14.9.

1-[1-(N-(Benzyloxycarbonyl)amino)-2-methylthioethyl]-2-hydroxy-3-(ethoxycarbonyl)-1,2,3,4-tetrahydro-β-carbolines (25). Product (**25**) was prepared from tryptamine (**19**) (0.25 g, 1.0 mmole) and aldehyde (**5**) (0.28 g, 1.1 mole) as described for the preparation of (**20**). Column chromatographic separation (silicagel, hexane/ethyl acetate, 5/1, v/v, eluent) gave (1S, 3R, 10S) (**25**) (0.09 g, 0.18 mmole, 18%), ^{1}H-NMR ($CDCl_3$) δ 8.8 (s, 1H), 7.5-6.8 (m, 10H), 6.1 (s, 1H), 5.0 (s, 2H), 4.7 (s, 1H), 4.6 (s, 1H), 4.3 (q, 2H), 3.9 (s, 1H), 3.1 (m, 2H) 2.9 (s, 2H), 2.1 (s, 3H), 1.3 (t, 3H); ^{13}C-NMR ($CDCl_3$) δ 172.9, 156.5, 136.1, 128.5, 128.5, 128.4, 128.1, 127.9, 127.6, 127.0, 122.1, 119.7, 118.0, 117.9, 111.5, 111.5, 67.9, 66.9, 61.7, 60.4, 36.4, 25.0, 21.1, 15.8, 14.2.

(±)-N(10)-Benzyloxycarbonyldebromoeudistomin L (26).

Method A: To a stirred refluxing mixture of water (0.2 m*l*), bromochloromethane (20 mg, 0.15 mmole), and triethylbenzylammonium chloride (TEBAC) (2 mg, 0.1 mmole), a solution of the (1S, 10S) and (1R, 10R) mixture of (**21**) (20 mg, 0.05 mmole), potassium hydroxide (8 mg, 0.14 mmole), and water (0.5 m*l*) was added dropwise under nigrogen at such rate that the addition was complete after 1 h. Stirring and refluxing were continued for 5 h. The mixture was then poured into water and extracted with diethyl ether. After drying over magnesium sulfate, he solvent was evaporated and the product (1S, 10S) and (1R, 10R) (**26**) (10 mg, 0.025 mmole, 50%) was obtained.

Method B: (1S, 10S) and (1R, 10R) (**26**) was also prepared from (1S, 10S) and (1R, 10R) (**21**) by treatment with dibromomethane and Adogen 464 (Aldrich Chem. Co.) as described above in 35% yield.

Method C: To a cooled (0℃) and stirred solution of (1S, 10S) and (1R, 10R) (**22**) (0.41 g, 1.0 mmole) in carbon tetrachloride (20 m*l*) was added N-chlorosuccinimide (NCS) (0.16 g, 1.2 mmole) over a period of 15 min. After the mixture was stirred for another 12 h at 0℃, concentration *in vacuo*. Insoluble succinimide was filtered off and washed several times with diethyl ether. The organic layer were washed with water, dried over magnesium sulfate, filtered, and evaporated to give an brown powder (0.4 g). Column chromatographic separation using preparative HPLC system (ODS column, methanol eluent) gave (1S, 10S) and (1R, 10R), (**26**) (29 mg, 0.07 mmole, 7%). ^{1}H-NMR ($CDCl_3$) δ 8.5 (s, 1H), 7.6-6.9 (m, 9H), 6.0 (d, 1H), 5.1 (s, 2H), 4.9 (d, 1H), 4.7 (d, 1H), 4.2 (s, 2H), 3.6 (t, 2H), 3.3 (d, 1H), 3.1 (m, 1H), 2.9 (t, 2H); ^{13}C-NMR ($CDCl_3$) δ 158.0, 137.8, 136.8, 131.0, 129.2, 129.0, 128.9, 128.4, 127.0, 122.7, 120.1, 118.7, 118.6, 112.1, 110.4, 71.7, 69.8, 67.3, 55.5, 50.2, 33.1, 21.3.

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NMR Relaxation Study of Segmental Motions in Polymer-*n*-Alkanes

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^{13}C spin-lattice relaxation times were measured for *n*-alkanes of moderate chain length, ranging from *n*-octane to *n*-dodecane, under the condition of proton broad-band decoupling within the temperature range of 248-318 K in order to gain some insight into basic features of segmental motions occurring in long chain ploymeric molecules. The NOE data showed that except for methyl carbon-13 dipole-dipole interactions between ^{13}C and directly bonded ^{1}H provide the major relaxation pathway, and we have analyzed the observed T_1 data on the basis of the internal rotational diffusion theory by Wallach and the conformational jump theory by London and Avitabile. The results show that the internal rotational diffusion constants about C-C bonds in the alkane backbone are all within the range of 10^{9}-10^{10} sec^{-1} in magnitude while the mean lifetimes for rotational isomers are all of the order of 10^{-11}-10^{-10} sec. Analysis by the L-A theory predicts that activation energies for conformational interconversion between *gauche* and *trans* form gradually increase as we move from the chain end toward the central C-C bond and they are within the range of 2-4 kcal/mol for all the compounds investigated.

Introduction

Elucidation of motional behaviors of relatively short chain molecules such as *n*-alkanes of moderate chain length in neat liquid or dissolved state has eagerly been pursued by molecular scientists because it provides the basis of understanding of local segmental motions in more complex polymer molecules including biopolymers as well as synthetic ones. Despite great efforts by many investigators, however, fluxional nature of the structures of these chain molecules has thus far defied our attempts to describe their motional behaviors quantitatively in terms of simple dynamical models. The motions of each segment in these molecules are not fully independent of those of other segments in contrast to the case of small molecules. Instead, they are cooperatively coupled to one another in a complicated manner as is manifested by kink formation and propagation.[1-3] In order to make the analysis of these complicated motions mathematically tractable one usually treat the problem as that of multiple internal rotations about the skeleton σ bonds, which in-