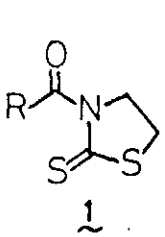
ORGANIC SYNTHESIS UTILIZING THIAZOLIDINE AND THE RELATED HETEROCYCLES

Eiichi Fujita
Institute for Chemical Research, Kyoto University, Uji, Kyoto-fu 611
Japan

Abstract ——— A highly selective asymmetric induction into symmetrical molecules having prochirality has been developed by utilizing 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione. In the model experiments of total synthesis of viginiamycin M2, the derivatives of 1,3-oxoazolidine-2-thione and 1,3-thiazolidine-2-thione were utilized effectively.

1. INTRODUCTION ——— UTILIZATION OF ATT

A very useful electrophilic amide, ATT (3-acyl-1,3-thiazolidine-2-thione) (1) has been developed by the author's research group. This compound has been shown to be an activated amide, whose carbonyl group is subject to the nucleophilic attack by several nucleophiles. For instance, several amines attack the amide carbonyl group and aminolysis takes place very smoothly under mild conditions.[1] We have synthesized spermidine amide alkaloids, *i. e.*, codonocarpine (2)[2], lunarine (3)[3], and lunaridine (4)[3], a spermidine siderophore, parabactin (5)[4], and new hypoxic cell radio-sensitizers FNT-1 (6) and FNT-2 (7)[5] utilizing this aminolysis as the key reaction.



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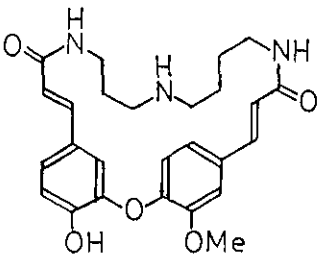

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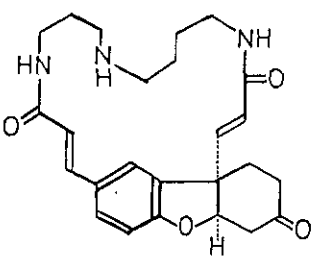

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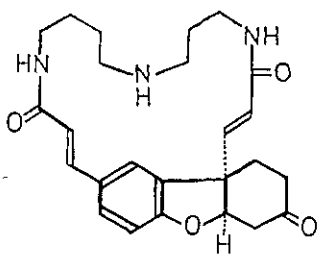

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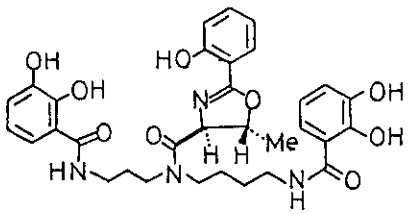

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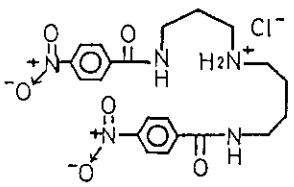

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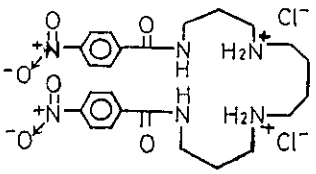

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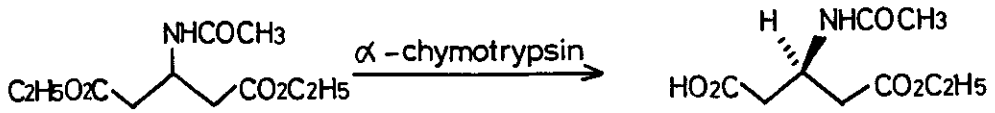
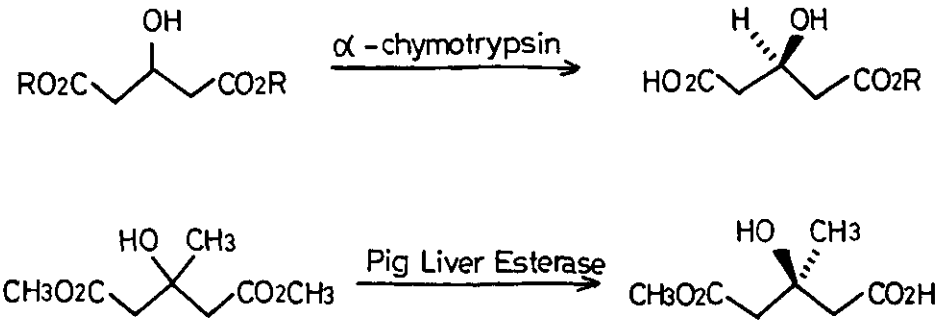
Aminolysis of ATT (1) was also utilized for synthesis of peptides[6] and several macrolactams.[7] In this reaction, the end point of the reaction can be easily recognized by the disappearance of the original yellow color of ATT. This is a very convenient point; one can monitor this reaction.

2. A NEW CHIRAL INDUCTION ——— UTILIZATION OF 4(*R*)-MCTT

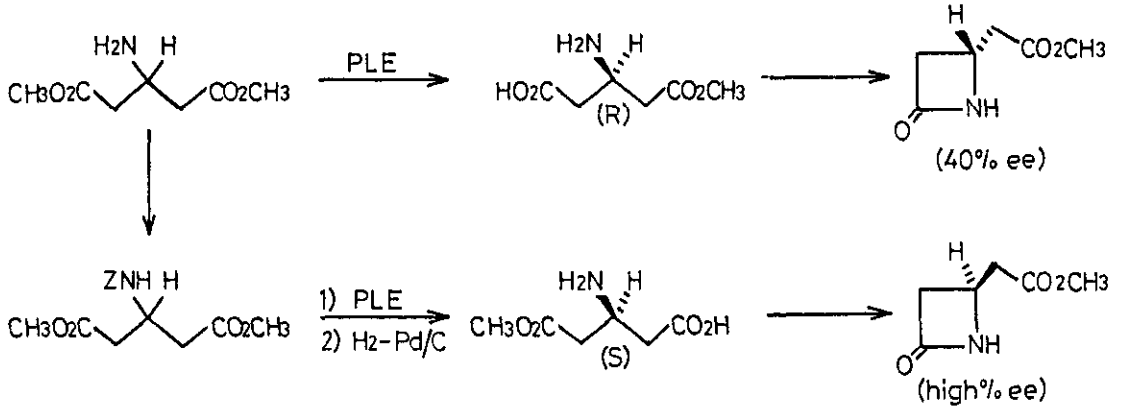
Recently, the utilization of optically active, simple acyclic compounds has been increasing, because they can be useful as the important starting resources for the total synthesis of biologically active natural products, such as macrolides, macrolactams, polyether antibiotics, β-lactam antibiotics and prostaglandins. Several acyclic compounds having optical activity have been obtained by degradation of natural products, such as sugars, amino acids, terpenes, *etc.*, or by enzymatic or microbiological syntheses, or by chemical asymmetric syntheses.

Highly selective transformations of enantiotopic group attached to a prochiral center in a symmetrical molecule such as 3-substituted glutaric acid derivative have been performed exclusively by some special enzymes. For instance, α-chymotrypsin catalyzes the highly selective partial hydrolysis of diethyl 3-acetamidoglutarate[8] and dimethyl- and diethyl 3-hydroxyglutarates.[9] Pig liver esterase also hydrolyzes highly selectively dimethyl 3-hydroxy-3-methyl-glutarate.[10]



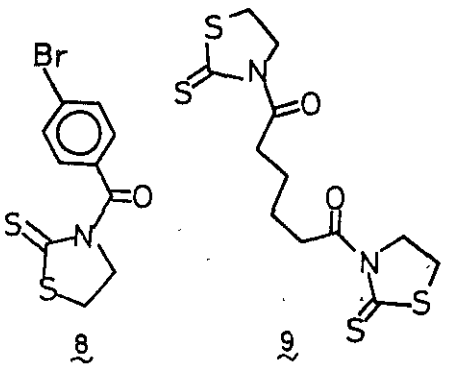


Pig liver esterase was also shown to catalyze the partial hydrolysis of dimethyl 3-amino- and 3-benzyloxyaminoglutarats[11]; β-lactams were derived as the optically active form.



We intended to develop a new chiral induction procedure by a purely chemical method. Previously, we synthesized amide 8[12] and diamide 9,[13] which were subjected to the X-ray crystallographic analysis. As the result, the carbonyl group and the thiocarbonyl group were shown to have nearly opposite orientation each other, because of their dipole-dipole repulsion. Furthermore, in the diamide 9, the shape of the molecule was shown to be nearly stretched due to repulsion between two heterocycles. These observations were very useful for design of a new molecule for chiral induction.

Thus, we designed a new model compound 10,[14] that is, diamide of 3-methylglutaric acid with 4(*R*)-methoxycarbonyl-1,3-thiazolidine-2-thione [4(*R*)-MCTT]. In this molecule, the fairly strong dipole-dipole repulsion between the thiocarbonyl and



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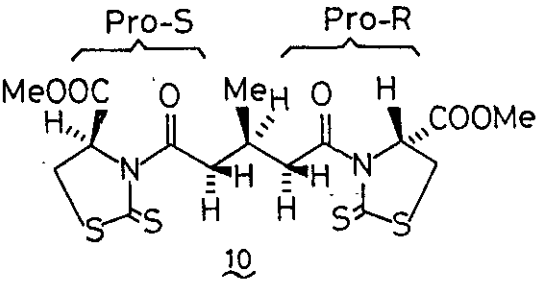

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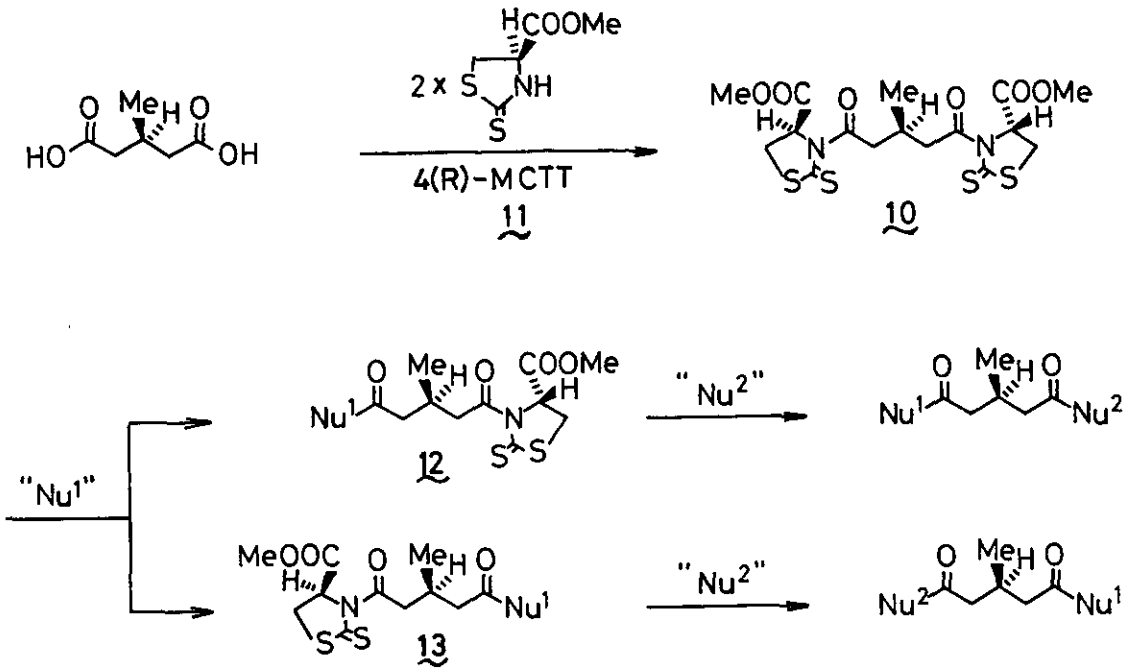
the amide carbonyl groups and the repulsion between pro-*S* and pro-*R* groups may regulate the stereochemistry of this compound to stabilize a favorable W-shape or a slightly twisted W-shape conformation especially at low temperature. In the assumed W-shape structure, the α-face of the carbonyl group in pro-*S* ligand should be least hindered in comparison with other three faces; the β-face of same carbonyl group is hindered by both β-methoxylcarbonyl 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 said carbonyl group is hindered by the α-methoxycarbonyl group; but the α-face of the carbonyl group in the pro-*S* ligand is hindered by neither methoxycarbonyl nor methyl groups, the substituents being β-oriented. Therefore, a suitable nucleophile may preferably attack the carbonyl group in the pro-*S* ligand from the least hindered α-face in the transition state.

An overall sequence of our method is shown in Scheme 1. It is quite difficult under usual chemical conditions to distinguish the pro-*S* ligand from the pro-*R* ligand of 3-methylglutaric acid. However, in the molecule of the optically active diamide which was designed by ourselves, the sterical situation around the carbonyl groups in the pro-*S* and the pro-*R* ligands is different. According to the foregoing working hypothesis, the nucleophile may attack selectively from the α-face of the carbonyl group in the pro-*S* ligand to give compound 12 as the major product and compound 13 as the minor diastereomer. The second attack of the other nucleophile should occur as shown in Scheme 1.



Scheme 1

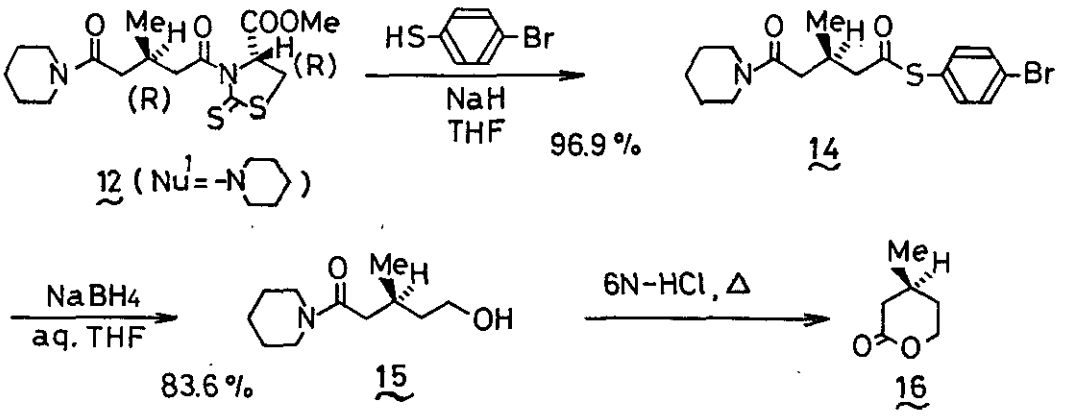
First, aminolysis of the key compound 10 which was prepared as usual (*vide post*) was tried in CH_2Cl_2 with one molar equivalent of several amines at room temperature or at -30°C, in order to find the best nucleophile Nu^1. The ratio of two diastereomers in the product mixture was checked by HPLC. The result showed that cyclic secondary amines displayed excellent regioselectivity, *i. e.*, 78 to 87% at -30°C. The best result was obtained with piperidine at -30°C. Thus, piperidine was used as Nu^1 in all of the following experiments.

The key compound 10 was prepared by the treatment of 3-methylglutaric acid with two molar equivalents of 4(*R*)-MCTT (11) in the presence of DCC in pyridine. Then this diamide was subjected to aminolysis with one molar equivalent of piperidine in CH_2Cl_2 at -30°C to give a mixture of diastereomers in 73.6% yield. The mixture was chromatographed on a silica gel column with elution by a mixture of hexane, ether, and ethyl acetate in a ratio 2 : 2 : 1 to give a pure major

product 12 (Nu^1 = -N◯) as crystals, mp 95.5 - 96°C, and a pure minor product 13 (Nu^1 = -N◯) as an oil in a ratio 88 : 12.

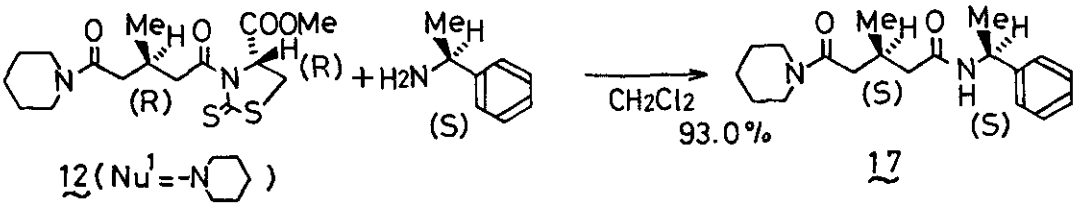
The 4(*R*)-MCTT (11) is synthesized from condensation of *l*-cysteine methyl ester with carbon disulfide. If *d*-cysteine methyl ester is used instead of *l*-compound, then 4(*S*)-MCTT is synthesized. If one uses this (*S*)-enantiomer, a completely reversed result will be obtained. Then, one will get the enantiomer of the compound 12 (Nu^1 = -N◯) as the major product and the enantiomer of the compound 13 (Nu^1 = -N◯) as the minor product. According to the choice of the stereochemistry of MCTT, one can select the major product as one wishes. This is an excellent point of this method.

The structure and absolute configuration of the major product were determined as follows. The major product was allowed to react with *p*-bromobenzenethiol in the presence of NaH to give thioester 14, whose reduction with $NaBH_4$ gave alcohol 15. The alcohol was treated with hydrochloric acid to give a lactone which was proved to be (-)-(3*S*)-methyl-valerolactone (16). Thus the structure and absolute configuration of the major product were determined as 12 (Nu^1 = -N◯) (Scheme 2).



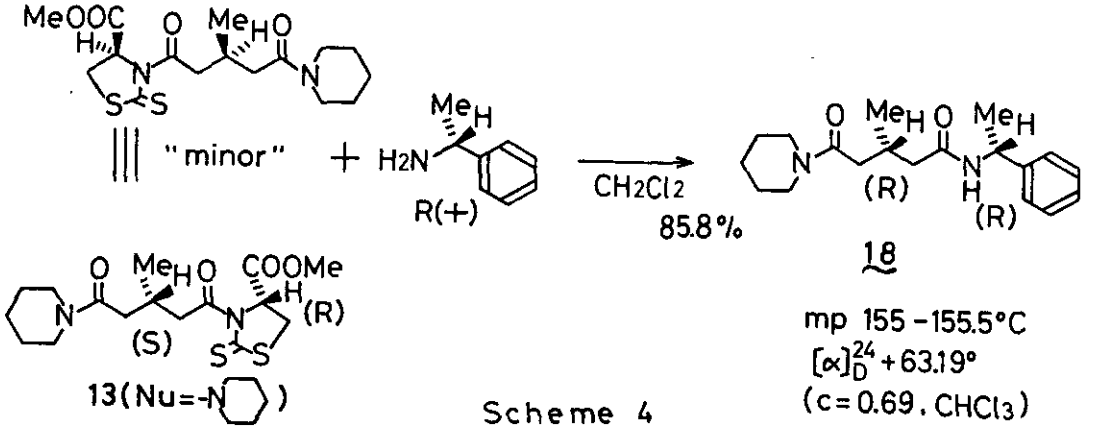
Scheme 2

Furthermore, this major product was subjected to aminolysis with (*S*)(-)-α-methylbenzylamine to give diamide 17, which was subjected to an X-ray crystallographic analysis. As the result, the structure and the relative stereochemistry were determined. On the basis of the known *S* configuration in the α-methylbenzylamine used, the absolute configuration of 17 was established. Thus the structure and the absolute configuration of the major product were confirmed again (Scheme 3).



Scheme 3

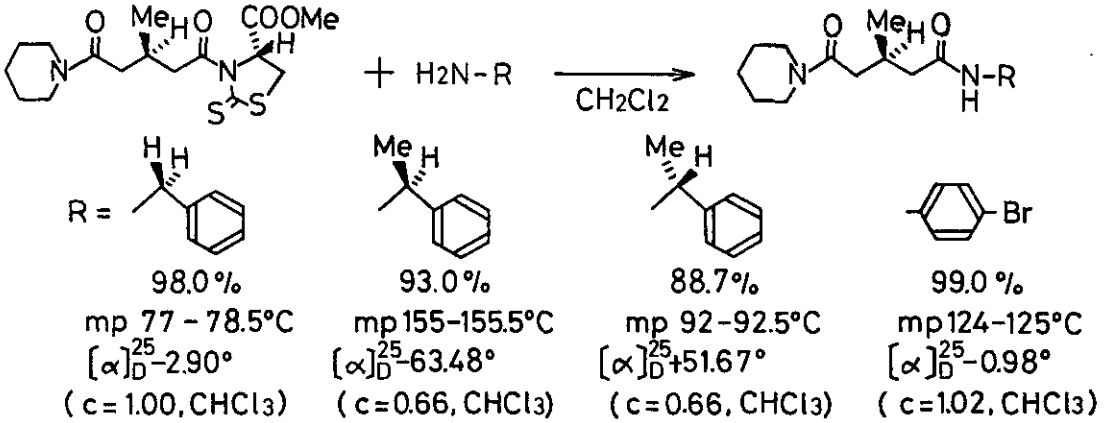
The structure and stereochemistry of the minor product were established by its transformation into diamide 18 *via* aminolysis with (*R*)(+)-α-methylbenzylamine. This compound 18 was proved to be the enantiomer of 17. Thus the minor compound was proved to be the (*S*)(*R*)-diastereomer of the major (*R*)(*R*)-product (Scheme 4).



Scheme 4

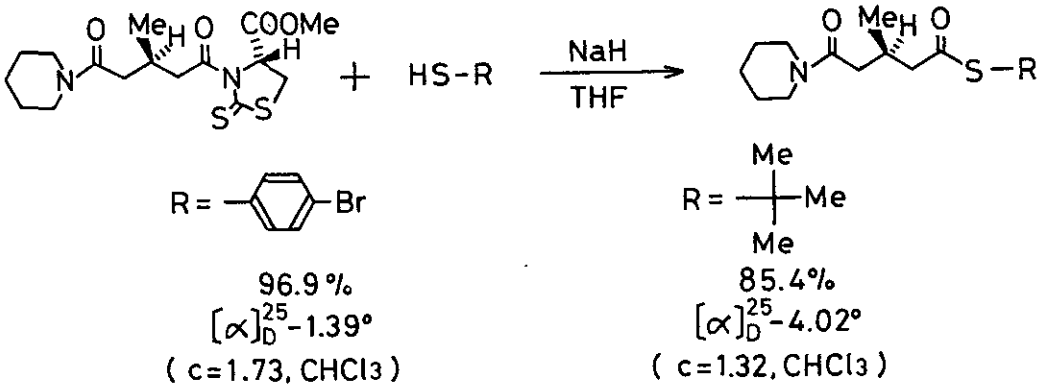
For the better understanding of this excellent differentiation, the original key compound, that is, 3-methylglutaric acid 4(*R*)-MCTT diamide (10) was subjected to an X-ray crystallographic analysis; its crystallographic structure was found to have a slightly twisted W-shpe conformation, supporting in principle our working hypothesis which led to this new chiral induction method.

Subsequently, the major product was subjected to the "monitored reaction" using several nucleophiles Nu^2. The Scheme 5 shows aminolysis with several amines. In every case, a high yield of the second step aminolysis product was given for an optically pure compound, respectively.



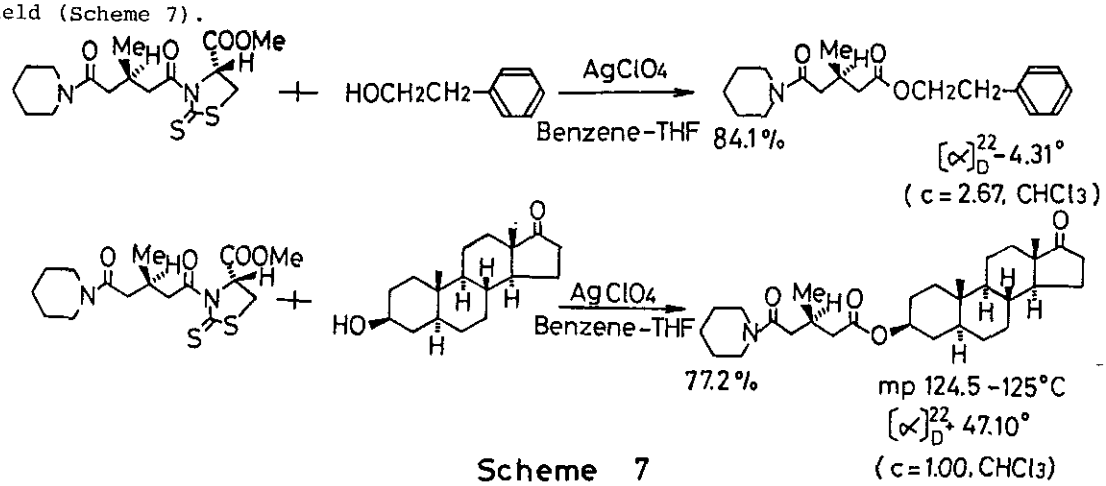
Scheme 5

Treatment of the major product with thiol in the presence of NaH afforded thioester in a high yield (Scheme 6).



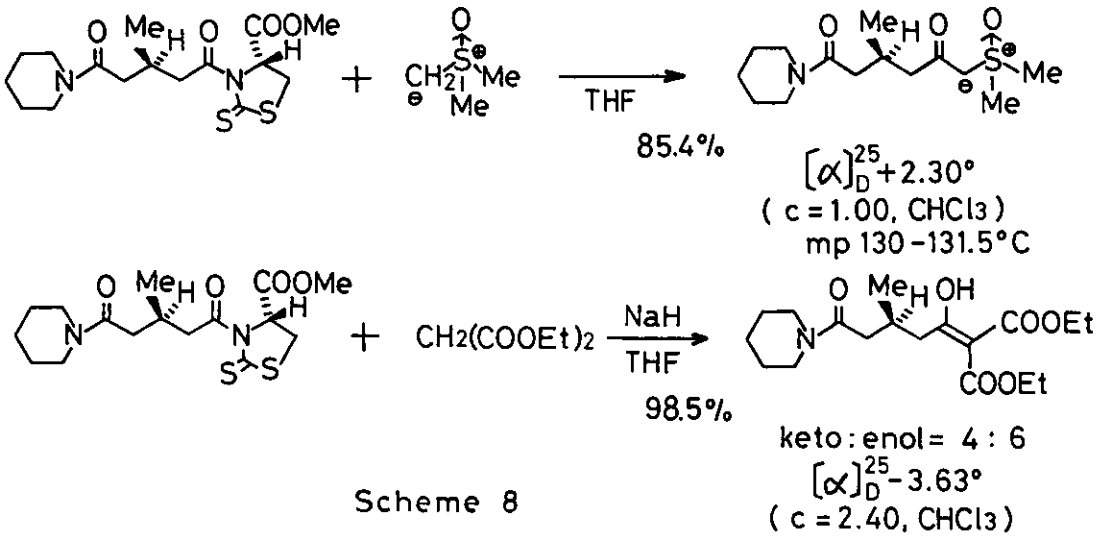
Scheme 6

Treatment of the major product with alcohol in the presence of NaH in THF or in the presence of $AgClO_4$ in a mixture of benzene and THF afforded ester in a high yield (Scheme 7).



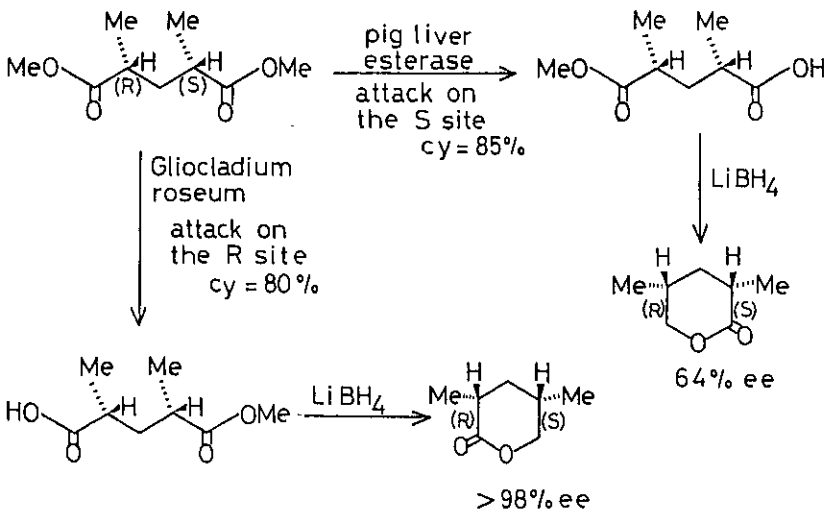
Scheme 7

Scheme 8 shows the reactions of the major product with dimethyloxosulfonium methylide and with diethyl malonate (+NaH). The C-C bond formation also takes place smoothly.



Scheme 8

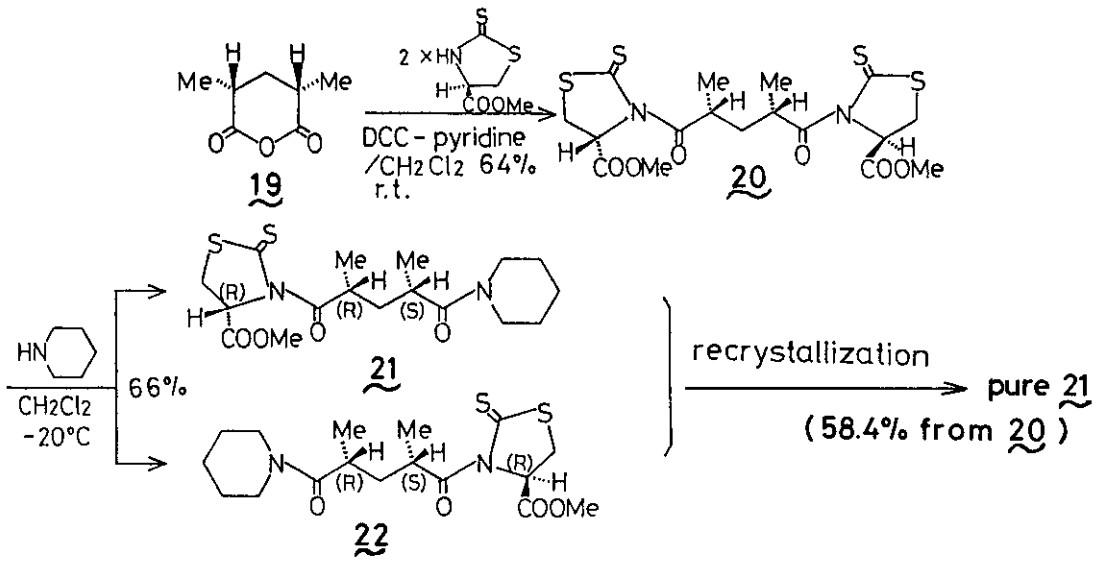
The highly stereoselective partial hydrolysis of dimethyl *meso*-2,4-dimethylglutarate has been performed by using a microorganism (Scheme 9).[15]



Scheme 9

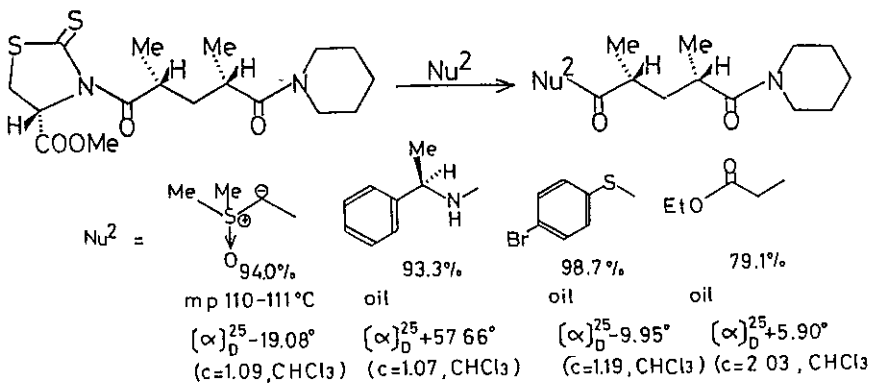
We extended our new chiral induction to *meso*-2,4-dimethylglutaric acid.[16] The *meso*-2,4-dimethylgluratic anhydride (19) was easily obtained from the *meso* and racemic mixture of 2,4-dimethylglutaric acid. The anhydride 19 was subjected to condensation with two molar equivalents of 2(*R*)-MCTT in the presence of DCC in pyridine to give a 64% yield of the key diamide 20. Then the first aminolysis of this compound with one molar equivalent of piperidine in CH_2Cl_2 at -20°C proceeded

smoothly and gave a mixture of diastereoisomers in a ratio 97.5 to 2.5, showing an almost quantitative selectivity. The ratio was determined by HPLC. Recrystallization of the mixture from CH_2Cl_2-petroleum ether only once gave a completely optically pure product as crystals, mp 111 - 112°C; $[\alpha]_D^{20}$ -113.78°. Its structure and absolute configuration were espablished by X-ray analysis as shown by the formula 21 (Scheme 10).



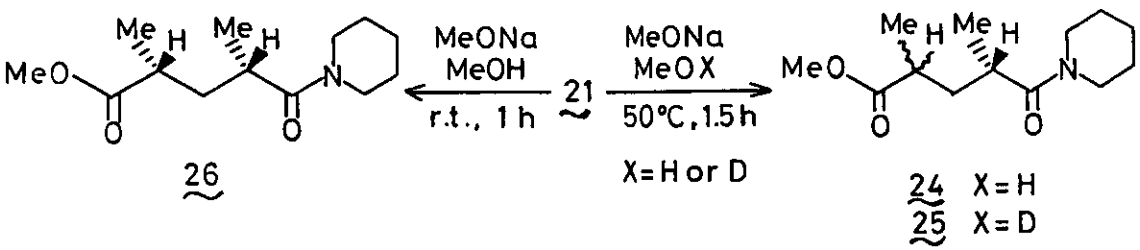
Scheme 10

The minor product was obtained abundantly as crystals; mp 135 - 135.5°C; $[\alpha]_D^{25}$ -46.35°, through another route[16] and its structure and absolute configuration were established as shown by formula 22 by X-ray analysis. The major product (21) was treated with several nucleophiles (Nu^2) to give optically pure acyclic products in high yields (Scheme 11).



Scheme 11

It was confirmed by the ^{1}H NMR (100 MHz) analysis of products (23) that no epimerization occurred at all during the transformation from 20 into 23. On the ^{1}H NMR chart of the epimerized product, 24 or 25, prepared under basic conditions at 50°C (Scheme 12), signals (δ 1.08, 1.10, J = 7 Hz each) assignable to the methyl protons at C-4 were observed as two doublets. On the other hand, the ^{1}H NMR spectra of 23 and 26 formed under mild basic conditions showed a sharp doublet signal due to the methyl protons at C-4.



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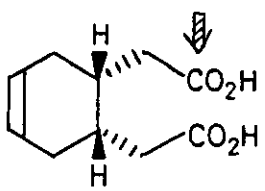
24 X=H
25 X=D

Scheme 12

Subsequently, *meso*-cyclohexene-4,5-diacetic acid (27), *meso*-cyclohexane-1,2-diacetic acid (28), and *meso*-5-norbornene-endo-2,3-diacetic acid (29) were converted into their 4(*R*)-MCTT diamide. Piperidine was found to attack the carbonyl group shown by an arrow highly selectively.[17]



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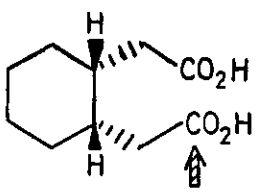

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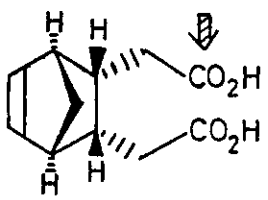

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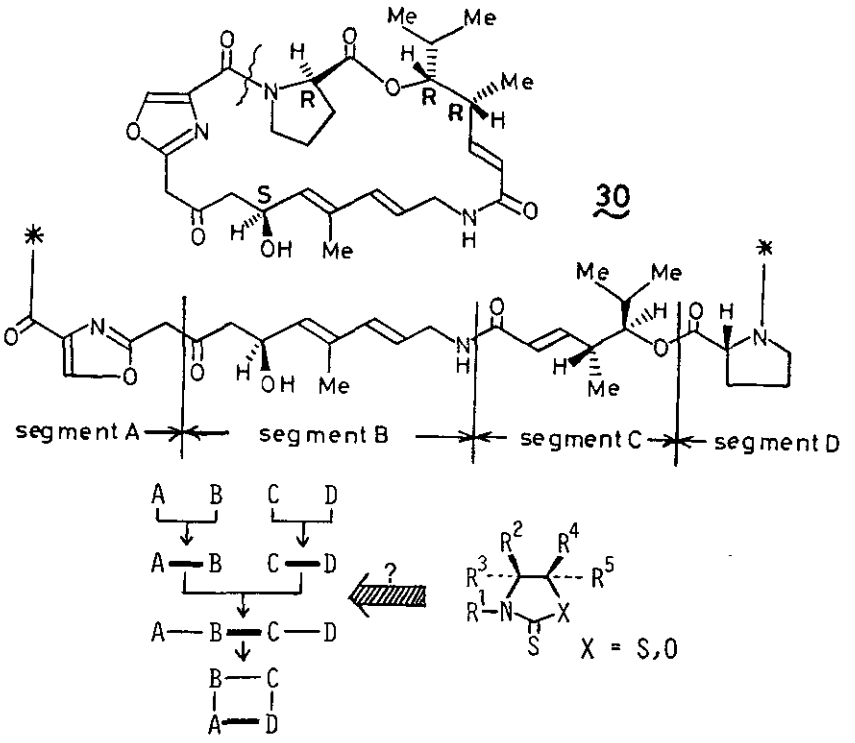
Thus, we established a new concept that the introduction of the two same chiral ligands [our case: two 4(*R*)-MCTT groups] into a prochiral compound having a symmetry plane changes its original symmetrical environment into an unsymmetrical environment.

3. APPROACH TO TOTAL SYNTHESIS OF VIAGINIAMYCIN M2

——— UTILIZATION OF TT, MPOT, AND TTPPA

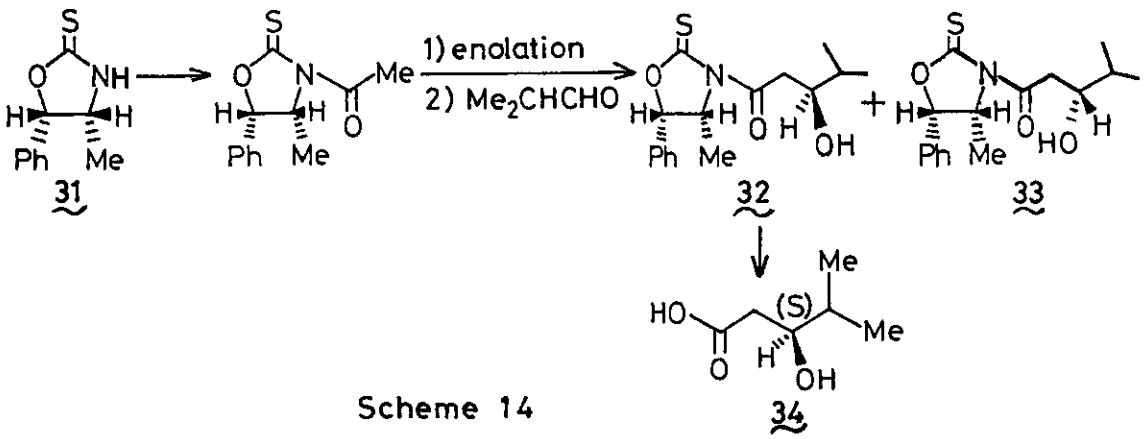
Recently, the investigation towards total synthesis of virginiamycin M2 (30) started in my laboratory. Our tentative synthetic strategy is as follows: (1) Synthesis of four segments A, B, C, and D; (2) Condensations between segments A and B and between segments C and D; (3) Condensation between B and C; (4) Final cyclization between A and D (Scheme 13).



Scheme 13

The synthesis of the segment A has been achieved according to Conforth's method.[18] The highly stereoselective asymmetric synthesis of β-hydroxy carboxylic acid part in the segment B is an important problem. We tried an asymmetric aldol condensation utilizing an optically active functional heterocycle, 4(*R*)-methyl-5(*S*)-phenyloxazolidine-2-thione (MPOT) (31) as a chiral auxiliary. This heterocycle was

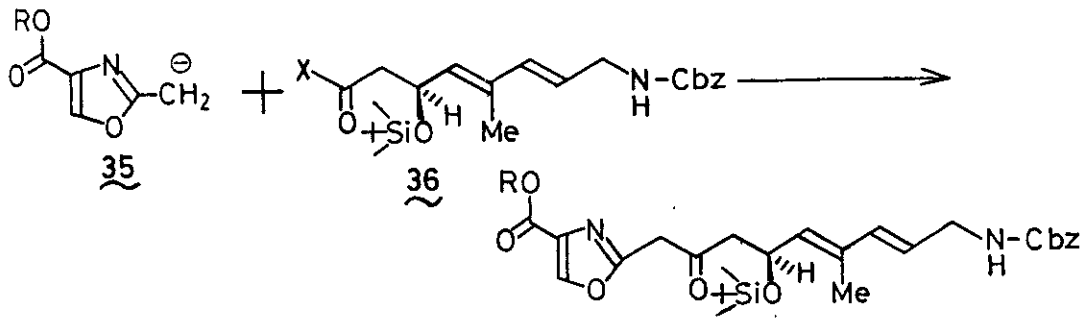
synthesized from condensation of norephedrine with carbon disulfide in THF. 3-Acetyl-4(*R*)-methyl-5(*S*)-phenyloxazolidine-2-thione (AMPOT) was prepared by N-acetylation of MPOT and was enolated by stannous trifluoromethanesulfonate (triflate) and N-ethylpiperidine in dichloromethane at low temperature.[19] Subsequent treatment with isobutyraldehyde gave a mixture of diastereomers 32 and 33 in a ratio 89 : 11 which was checked by HPLC. The mixture was chromatographed on a silica gel column to isolate the major product 32 as the optically pure compound in 68% yield.[20] The absolute configuration was confirmed by a comparison of the specific rotation value of its hydrolysate 34 with that shown in literature[21] (Scheme 14).



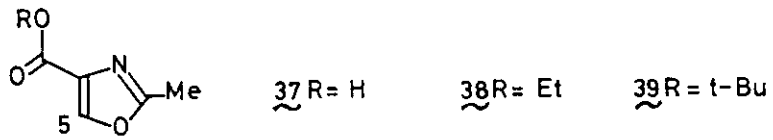
Scheme 14

Subsequently, 4(*S*)-ethyl-3-acetyloxazolidine-2-thione having an opposite configuration at the position 4 was enolated similarly and isobutyraldehyde was subjected to aldol condensation with this enolate to give a mixture of diastereoisomers in a ratio 91.4 : 8.6. The confirmation of the absolute configuration of the major product was made by the specific rotation value of the free acid. Thus, the enantiomer of 34 was highly selectively obtained.[20]

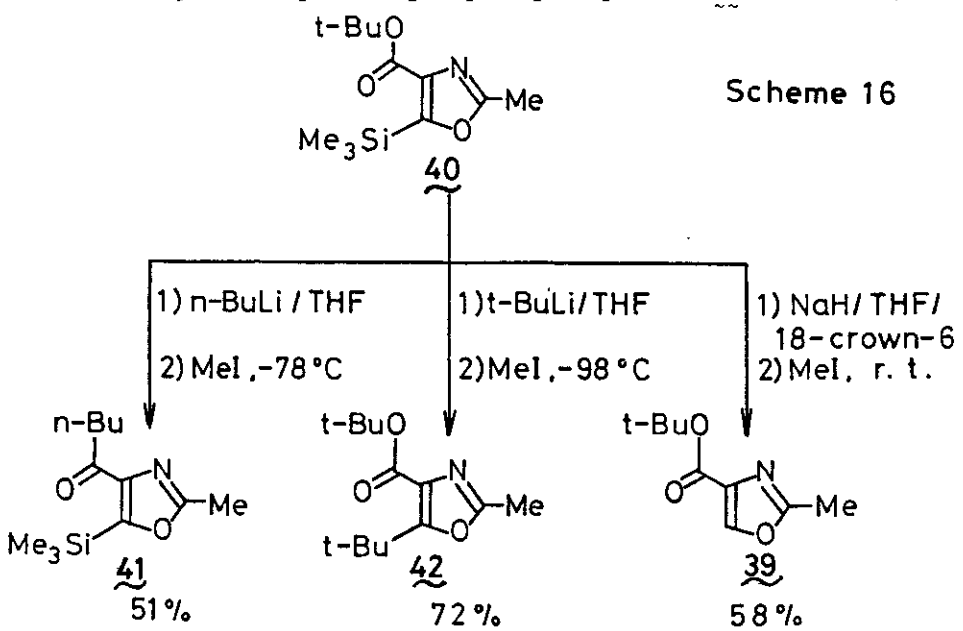
The next problem is the C-C bond formation between segments A and B.[22] Our first strategy was in the condensation between anionic segment A (35) and active carbonyl compound 36 (Scheme 15). We first tried acylation at the C-2 methyl group of carboxylic acid 37, its ethyl ester 38, and its *t*-butyl ester 39 under several metal-containing basic conditions. But, undesirable results were encountered, similarly to the case of Meyer's group.[23,24] ; the C-5 was metalated exclusively in 37 and 39.



Scheme 15

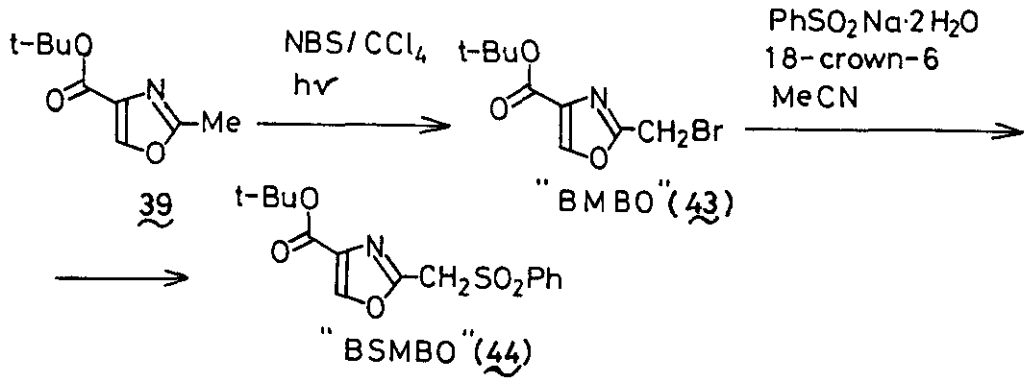


Hence, a C-5 protecting derivative, 4-*t*-butoxycarbonyl-2-methyl-5-trimethylsilyl-1,3-oxazole (40), was prepared from 39 by treatment with trimethylsilyl chloride. On treatment with *n*-BuLi at -78°C in THF under argon gas and then with MeI, compound 40 gave an unexpected ketone 41, instead of the desirable product methylated at the 2-methyl group. The similar treatment of 40 with *t*-BuLi at -98°C followed by MeI afforded an unusual Michael-type addition product 42 in good yield under elimination of the trimethylsilyl group. Compound 40 was stirred with NaH in THF in the presence of 18-crown-6 at room temperature under nitrogen, and treated with MeI to give unexpected hydrogenolysis product 39 (Scheme 16).



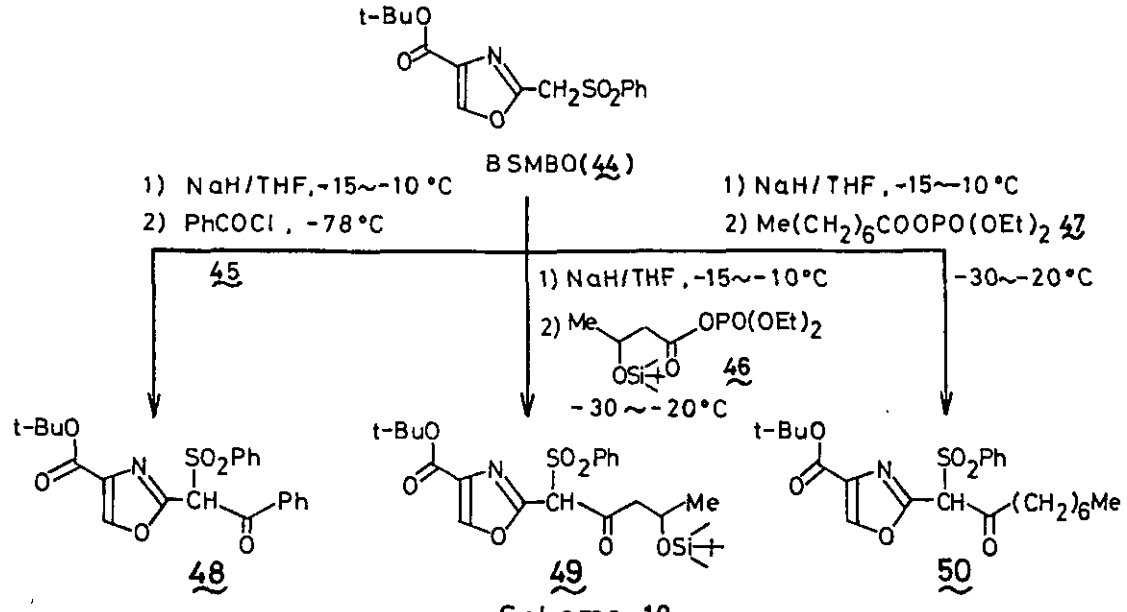
Scheme 16

Then, the compound 39 was brominated with NBS in CCl_4 under irradiation in the presence of catalytic benzoyl peroxide to give 2-bromomethyl-4-*t*-butoxycarbonyl-1,3-oxazole (BMBO) (43), which was subjected to benzenesulfonylation under the presence of catalytic 18-crown-6 to afford 2-benzenesulfonyl-methyl-4-*t*-butoxycarbonyl-1,3-oxazole (BSMBO) (44) (Scheme 17).



Scheme 17

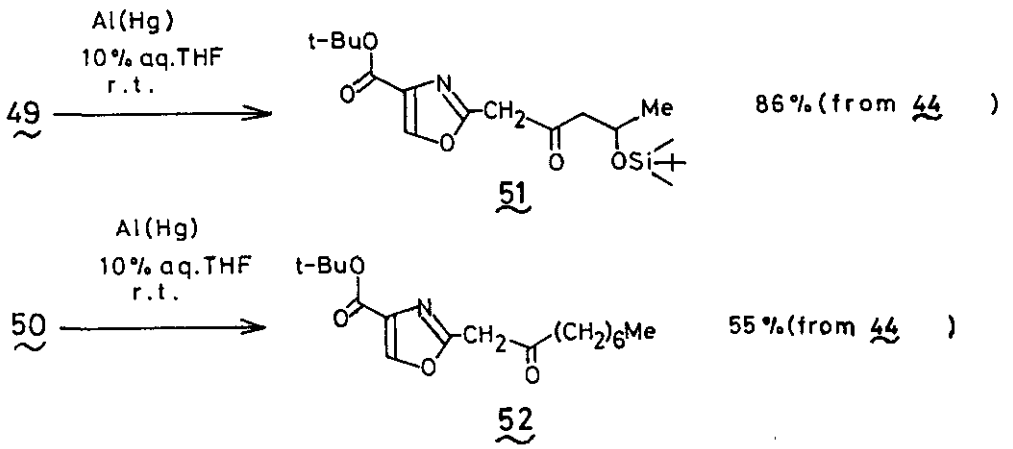
BSMBO (44), dissolved in THF in the presence of NaH, was treated with acylating electrophile 45, 46, or 47 at low temperature to afford the corresponding desirable product 48, 49, or 50, respectively (Scheme 18).[22]



Scheme 18

Without purification, compounds 49 and 50 were subjected to the reductive desulfonylation with Al(Hg) in 90% THF - 10% H_2O mixture at room temperature to give the desirable products 51 and 52, respectively (Scheme 19).[22] Synthesis of 52

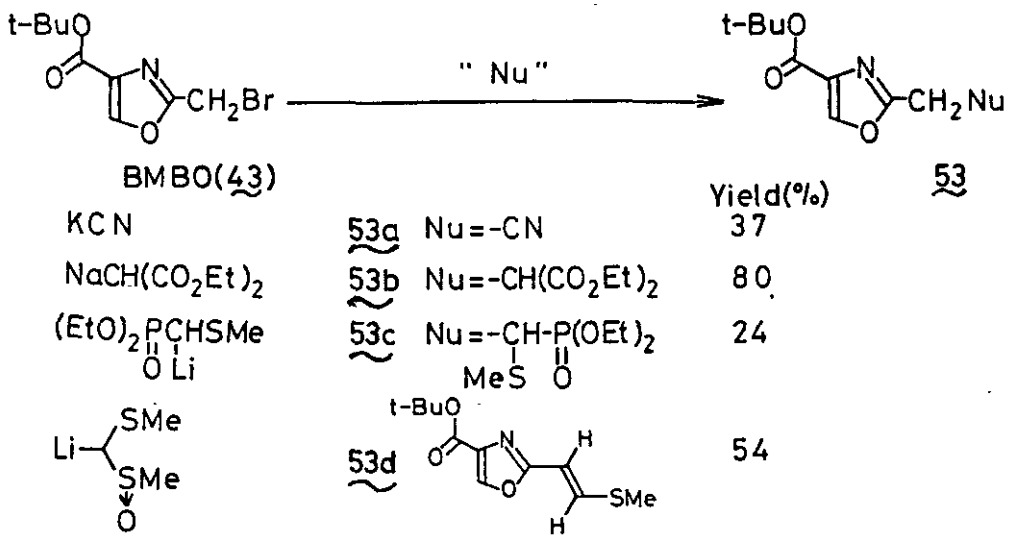
forms an important model experiment for construction of the oxazole moiety of virginiamycin M2.



Scheme 19

Thus, BSMBO-carbanion was shown to be equivalent to the anion 35 (R = *t*-Bu).

Subsequently, the substitution reactions of BMBO (43) with some carbanions were investigated. The desirable products 53a ∿ 53d were obtained in various yields, respectively (Scheme 20).[25]

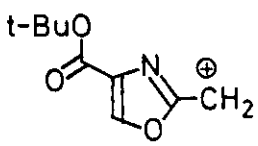


Scheme 20

Several substitution reaction of BMBO (43) with sulfide, oxide, and iodide anions. Desirable products 53e ∿ 53k were obtained.

53e	Nu = -OOCMe	Yield (%)	82
53f	-OH		32
53g	-SPh		81
53h	-S-(2-pyridyl)		78
53i	-S-(1-Me-2-imidazolyl)		69
53j	-S(=O)-Ph		76
53k	-I		80

Sulfone 53j is a notable compound for construction of the C-C bond between segments A and B. The compounds 53g ~ 53i were oxidized with *m*-chloroperbenzoic acid to give the corresponding sulfoxides, which will be similarly useful for the same purpose. Thus BMBO (43) can be utilized as the cationic synthon 54.[24]



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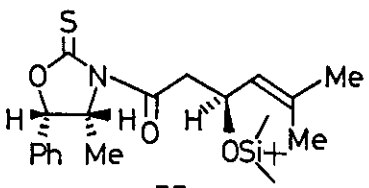

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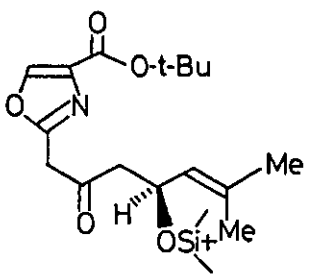
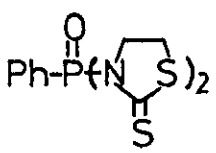


56

A model experiment was carried out by the condensation of asymmetrically synthesized model compound 55 with BSMBO anion and subsequent reductive desulfonylation of the resulting product afforded the desired compound 56.

Asymmetric synthesis of β-hydroxy-α-methyl aldehyde system in the segment C was carried out by the aldol condensation between enolate of 3-propionyl homolog of AMPOT and isobutyraldehyde followed by protection of the secondary alcohol and subsequent treatment with diisobutylaluminum hydride. The modified Wittig reaction (Horner, Wadsworth-Emmon's modification) converted aldehyde into α,β-unsaturated carboxylic acid ester; thus the synthesis of the segment C was accomplished.

Amide bond formation between the segments B and C was investigated. As the result, thiazolidine-2-thione phenylphosphonamide (TTPPA) (57) was shown to be very useful. As a model experiment, we synthesized amide 58 effecfively. In this case, aminolysis of 3-acylthiazolidine-2-thione was not suitable, because amide 59 was not stable for purification.



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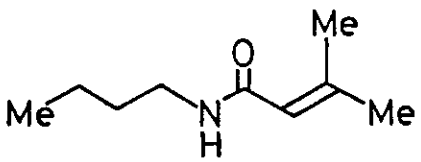

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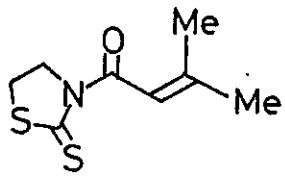

59

The same procedure was useful for amide bond formation between segments A and D.

Finally, the results obtained so far from our model experiments for the total synthesis of virginiamycin M2 are summarized as follows.

1. BSMBO was symthesized as an equivalent compound for the segment A.
2. An optically active functional heterocycle MPOT was utilized as a chiral auxiliary for the asymmetric synthesis of the α,β-unsaturated alcohol moiety in the segment B and of the chiral part in the segment C.
3. BSMBO anion was allowed to react with compound 55 to form a C-C bond where MPOT was utilized as a good leaving group in an activated amide.
4. TTPPA was utilized for the amide bond formation between the segments B and C and between segments A and D.

Thus, numerous problems for the total synthesis of virginiamycin M2 were solved in the model experiments. In these experiments, utilization of functional heterocycles such as TT, MPOT, and TTPPA was developed, which should be emphasized. The total synthesis of virginiamycin M2 itself is now in process in my laboratory on the basis of those useful findings.

In the first topic, it was described that development of a new heterocycle 4(*R*)-MCTT led to a new chiral induction procedure. Important role of these functional heterocycles in the field of organic synthesis will be increased more and more. Especially utility of the chiral heterocycles as the chiral auxiliaries will be increased.

ACKNOWLEDGEMENT

I thank my excellent coworkers, Dr. Y. Nagao, Mr. M. Yagi, Mr. T. Ikeda, Mr. T. Inoue, Mr. S. Yamada, and Mr. Y. Hagiwara. Dr. M. Shiro, Shionogi Co. Ltd. kindly carried out X-ray analyses for us. Thanks are also due to the financial support in part by Grant-in-Aid for Special Project Research supplied from the Ministry of Education, Science and Culture in Japan.

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