A NEW PRACTICAL SYNTHETIC METHOD: MONITORED AMINOLYSIS OF 3-ACYL-1,3-THIAZOLIDINE-2-THIONE†

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Abstract —— This review article deals with the monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione and its applications to the total synthesis of macrocyclic spermidine alkaloids, codonocarpine, (±)-lunarine, and (±)-lunaridine, and the peptide synthesis. Biological and physiological activities of 3-acyl-1,3-thiazolidine-2-thione are briefly described.

1. INTRODUCTION

Our recent interests have been focused on the systematic development of new reactions, which can be applicable for the synthesis of the physiologically active natural products. We have planned and executed new reactions, according to the philosophy which constructed the backbone of our desirable chemistry (see Fig. 1).

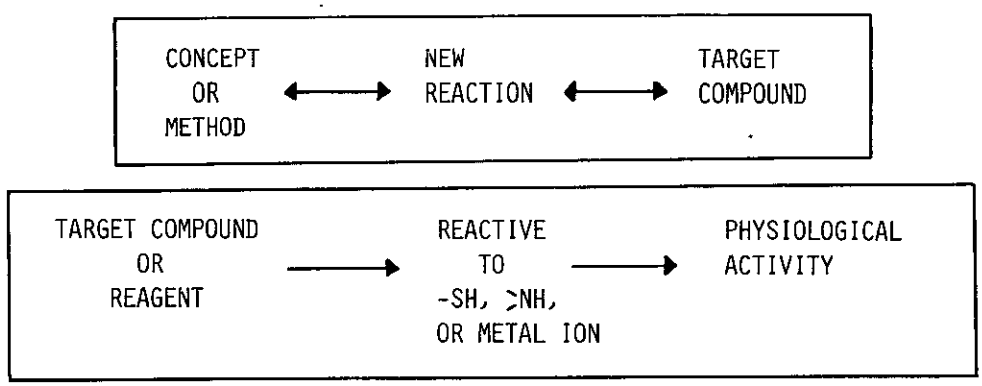


Fig.1

† Dedicated to Prof. Kyosuke Tsuda on the occasion of his 75th birthday.

The new reaction must be projected for the synthesis of a particular "target compound"; it must be based upon a particular "methodology" (e. g. utilization of sulfur-containing leaving group[1]) and/or a particular "concept" (e. g. Hard and Soft Acids and Bases Principle[2] or Umpolung[3]).

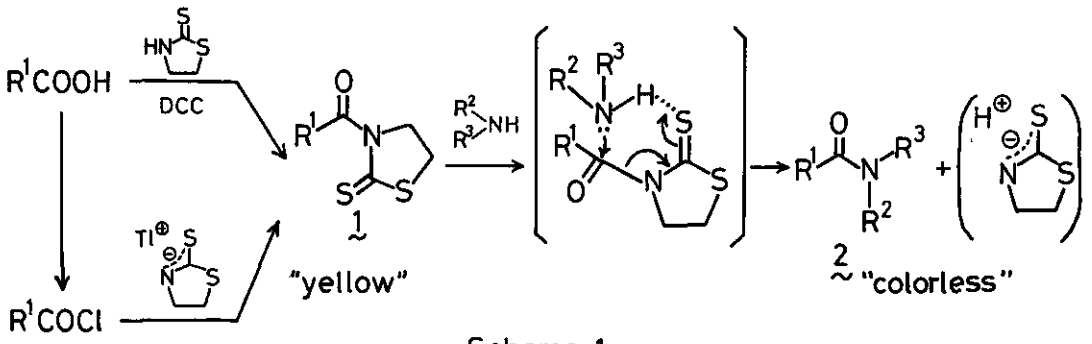
We choose and elaborate the target compound which is expected to be reactive to SH group, NH_2 group, or a special metal ion. Such a target compound would be expected to show interesting physiological activity.[4] We aim at development of new reactions and at search for new types of physiologically active compounds at the same time.[1]

Our recent target molecules are the N atom-containing substances, especially spermidin- or spermine-containing natural products (e. g. macrocyclic spermidine alkaloids,[5] sideropheres,[6] etc.), peptides, enzymes, and nucleic acids.

We are developing the new reactions utilizing the sulfur-containing leaving group.[1,7] Here we describe the features of the monitored aminolysis of 3-acyl-1,3-thiazolidine-2-thione (ATT) (1) and its applications to the total synthesis of some macrocyclic spermidine alkaloids and the peptide synthesis. Furthermore biological and physiological activities of several ATT (1) are discussed briefly.

2. SOME FEATURES ON THE MONITORED AMINOLYSIS OF ATT

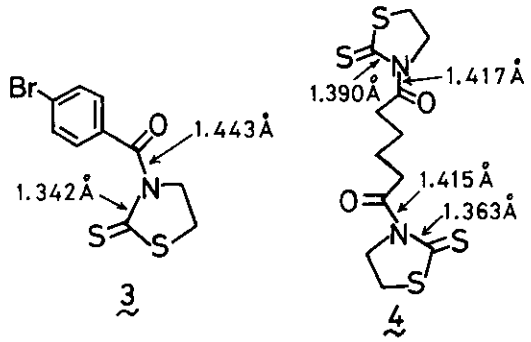
ATT (1) was subjected to the aminolysis under very mild conditions to give amide 2 in high yield (Scheme 1).[8] This reaction can be monitored conveniently by the disappearance of the original yellow color of the starting material 1.



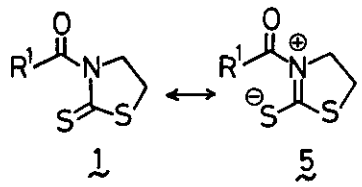
Scheme 1

The reason why ATT (1) is so highly reactive to such nucleophiles as amines, hydride ion, and arylcarbanion was solved by the X-ray analysis of compounds 3[9] and 4.[10] It clarified that they were not the usual amides but rather the activated carbonyl compounds having good leaving group(s), that is, 2-thionothiazolidino

group; bond lengths are as shown and the plane including the nitrogen atom and the one including the carbonyl group are twisted each other. In other words, contribution of the canonical formula 5 must be large and important.



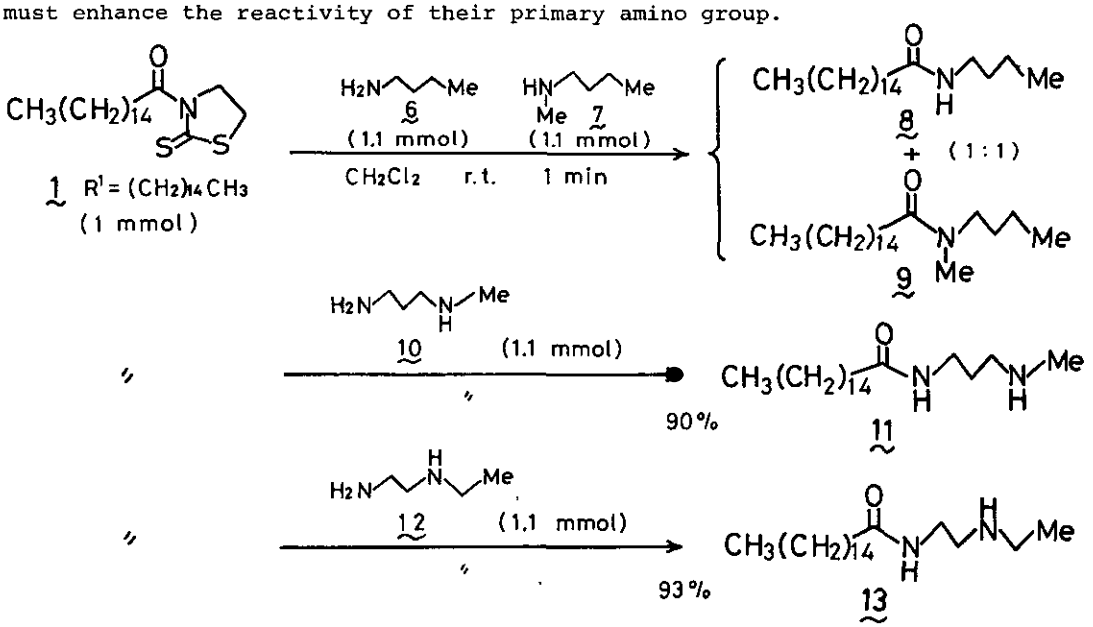
3 4



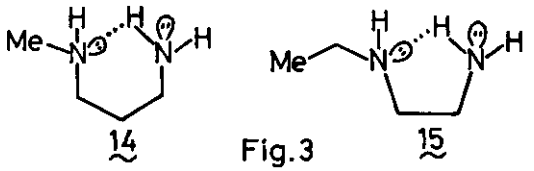
1 5

Fig. 2

Treatment of ATT (1) [$R^1 = (CH_2)_{14}CH_3$] with an equimolar mixture of n-butylamine (6) and n-butylmethylamine (7) gave a mixture of the corresponding hexadecanoyl amines 8 and 9 in a ratio 1:1 showing almost the same aminolysis rate between the primary amine and the secondary amine.[8] When ATT (1) [$R^1 = (CH_2)_{14}CH_3$] was similarly treated with diamine including an amino and an imino groups 10 or 12, however, hexadecanoyl amine 11 or 13 was obtained chemoselectively in high yield, respectively,[11] the imino group being kept intact. This may be due to a potential intramolecular hydrogen-bonding (14 or 15 in Fig. 3), as described by Krueger.[12] It must enhance the reactivity of their primary amino group.

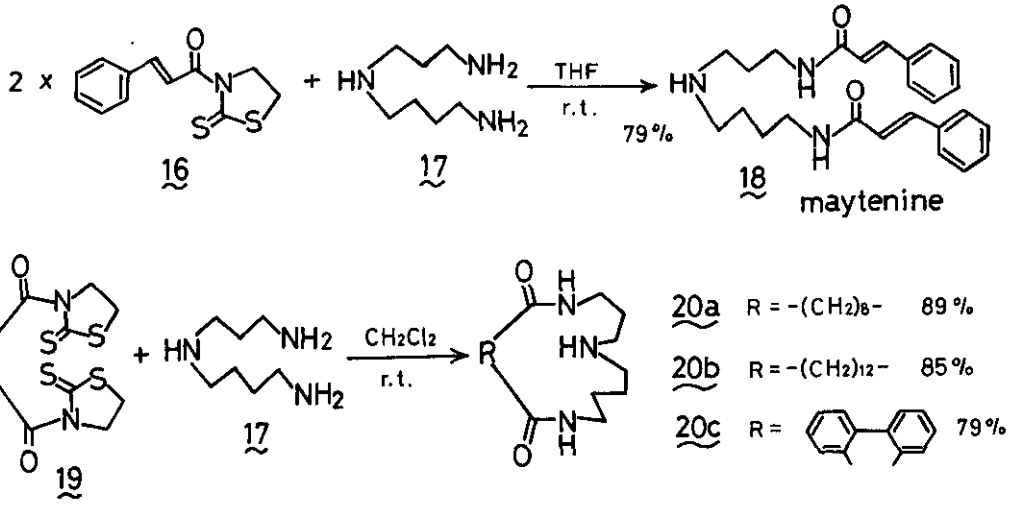


Scheme 2



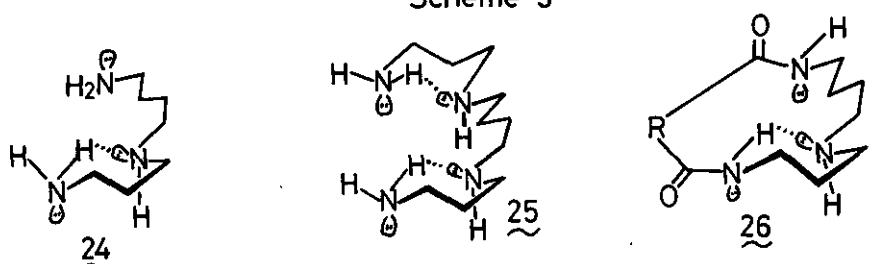
14 Fig.3 15

When compound 16, 19, or 21 was treated with spermidine 17 or spermine 22, the similar highly chemoselective aminolysis was observed to give the corresponding primary amine amide 18, 20a~c, or 23, respectively. (see Scheme 3).[8,13,14] These are also rationalized by the intramolecular hydrogen-bonding(24~26 in Fig. 4) in spermidine 17, spermine 22, or the amide products. This information was very useful for the synthesis of macrocyclic spermidine alkaloids (vide Post). It will be also useful for the synthesis of spermidine siderophore 27.[6]



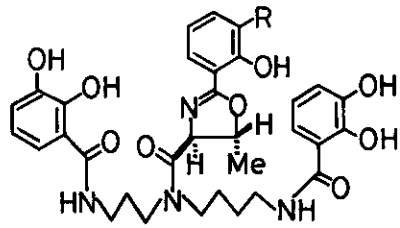
16 17 18 19 20a 20b 20c 21 22 23

Scheme 3



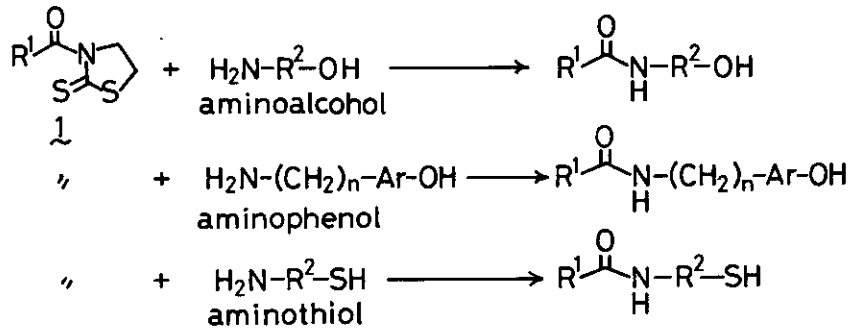
24 25 26

Fig. 4

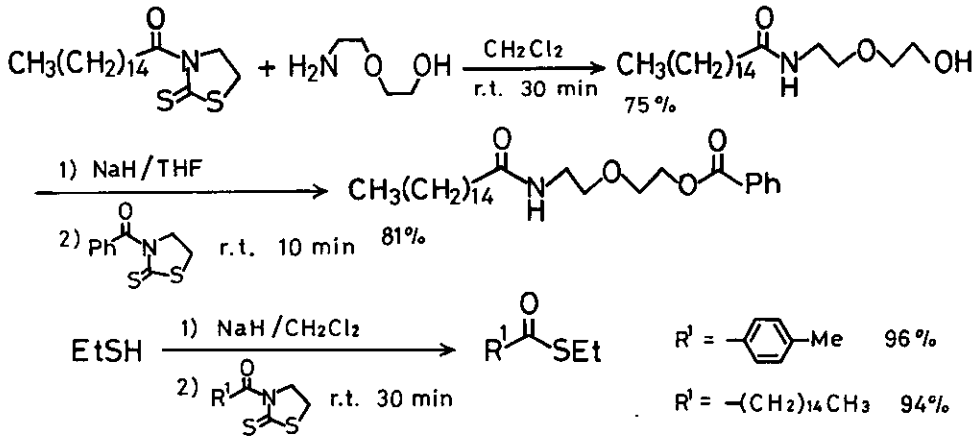


27 R = H or OH

ATT (1) shows also a high chemoselectivity for amine, as summarized in Scheme 4.[8,15] ATT (1) usually does not react with SH group and OH group. However, thioester or ester is easily obtainable from ATT (1) and thiol or alcohol in the presence of NaH (Scheme 5). This chemoselectivity was useful for the peptide synthesis (vide post).



Scheme 4

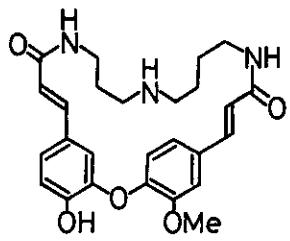


Scheme 5

3. TOTAL SYNTHESIS OF MACROCYCLIC SPERMIDINE ALKALOIDS, CODONOCARPINE,[16] (±)-LUNARINE,[17] AND (±)-LUNARIDINE[17]

In recent years, the biochemical studies on polyamines (spermidine, homospermidine, and spermine) have been extensively developed.[18] Many alkaloids containing such polyamines have also been isolated from plants; most of these alkaloids have a macroring system.[5]

Codonocarpine (28) was isolated from Codonocarpus australis A. Cunn. (Phytolaccaceae) by Doskotch and co-workers.[19] Its unique 24-membered macrocyclic diamide structure consists of spermidine and oxygeneted cinnamoid biphenyl ether moiety. Lunarine (29) and lunaridine (30) were isolated from Lunaria biennis (Cruciferae) by Potier and his group.[20] Its 20-membered macrocyclic diamide structure also consists of spermidine and Pummerer ketone derivative moiety. These alkaloids are suitable as the target compounds for utilizing the monitored aminolysis of ATT (1).



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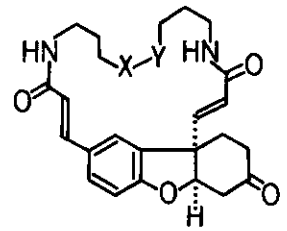


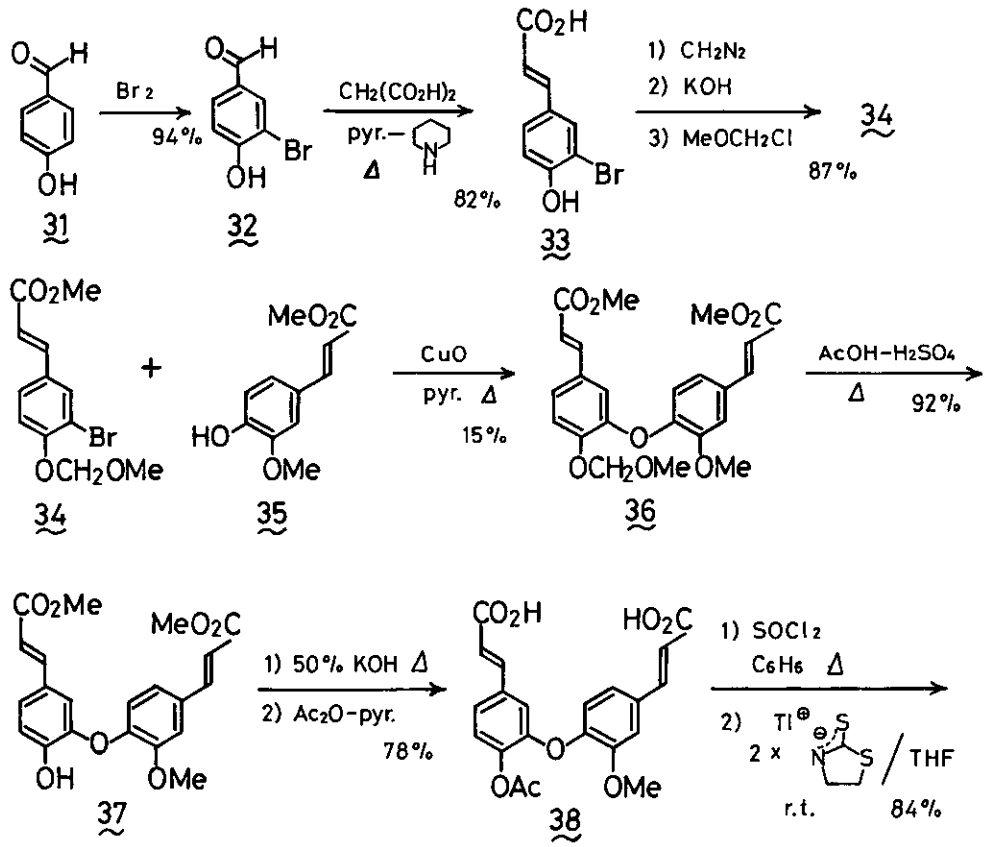
29 X = NH, Y = CH_2

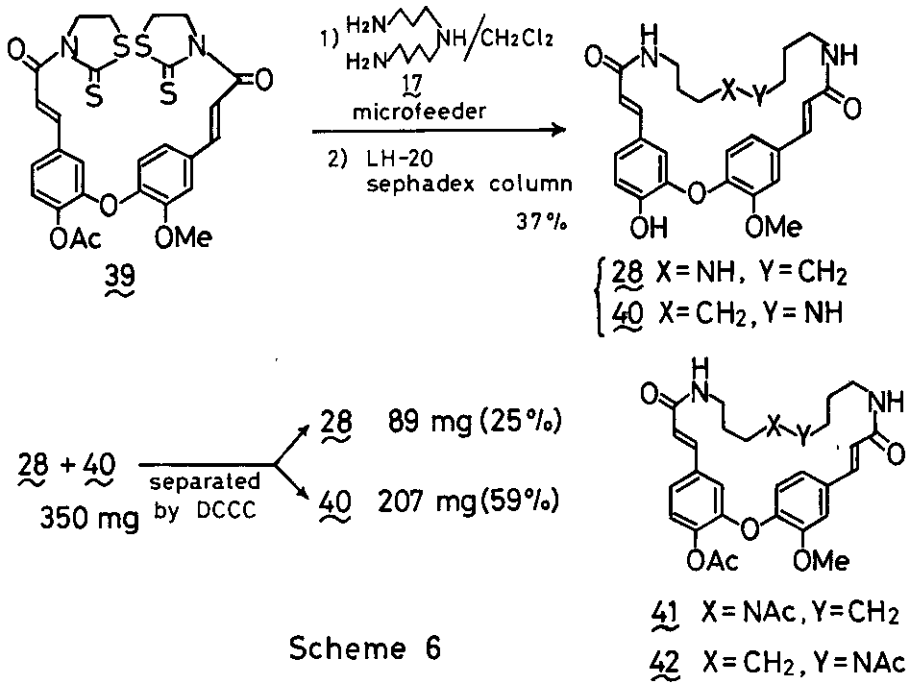
30 X = CH_2, Y = NH

The synthesis of codonocarpine (28) was carried out as follows. Bromination of p-hydroxybenzaldehyde (31), Knoevenagel condensation of the product 32 with malonic acid, selective methylation of carboxyl group of the product 33 followed by methoxymethylation of phenol transformed 31 into compound 34 in high yield. Ullmann condensation between 34 and methyl ferulate (35) was carried out in hot pyridine in the presence of CuO under the argon atmosphere to obtain the desired biphenyl ether 36. Deprotection of methoxymethyl group in 36, hydrolysis of the product 37 followed by acetylation gave dicarboxylic acid 38. Its acid chloride was treated with thallium (I) salt of 1,3-thiazolidine-2-thione to afford the desirable yellowish key-compound 39 in overall 84% yield from dicarboxylic acid 38. The cyclization between compound 39 and spermidine 17 was performed by the high

dilution method[13,14] using microfeeder to give a pale yellow crystalline mixture of codonocarpine (28) and its isomer 40 in 37% yield after purification on a sephadex LH-20 column by MeOH-$CHCl_3$ (7:3). Separation of the mixture was executed by the droplet countercurrent chromatography (DCCC) to afford pure codonocarpine (28) [mp 183-187° (decomp.)(from aqueous ammonia-MeOH)(lit.[19] mp 187° (decomp.); N,O-diacetylcodonocarpine (41), colorless fine needles, mp 166-170° (from acetone) (lit.[19] 169-171°)] as pale yellow fine prisms and its isomer 40 [mp 243-246° (decomp.)(from aqueous ammonia-MeOH); N,O-diacetate 42, colorless needles, mp 281-285° (decomp.) (from acetone)] as pale yellow prisms.

The accomplishment of this total synthesis was confirmed by the identity of melting point, retention time (HPLC), and spectral data (IR, PMR, and mass spectra) between synthetic and natural codonocarpine. The structure of the regioisomer 40 of codonocarpine was established by an X-ray analysis.[16] Quick and co-workers independently synthesized codonocarpine (28) at almost the same time.[21]

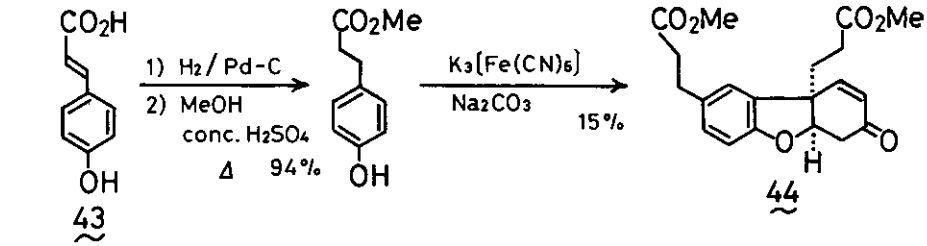


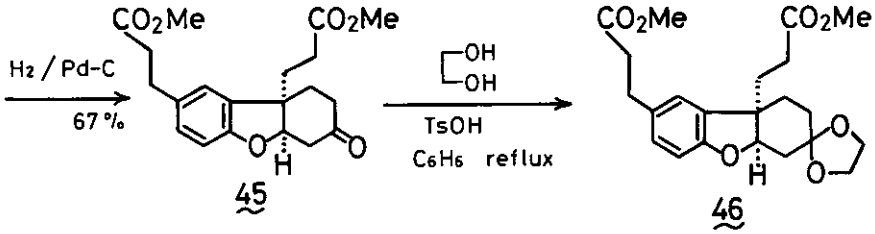


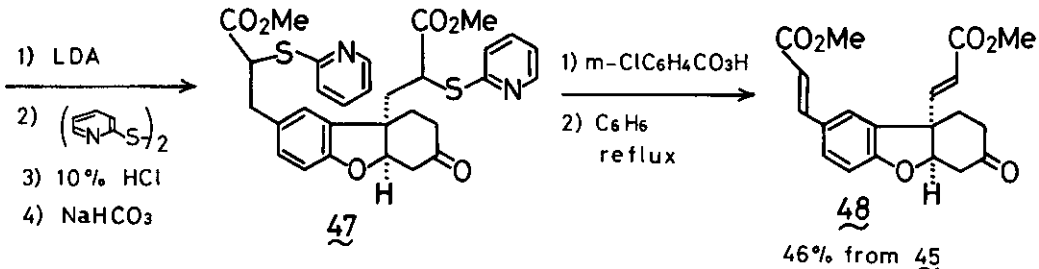
Scheme 6

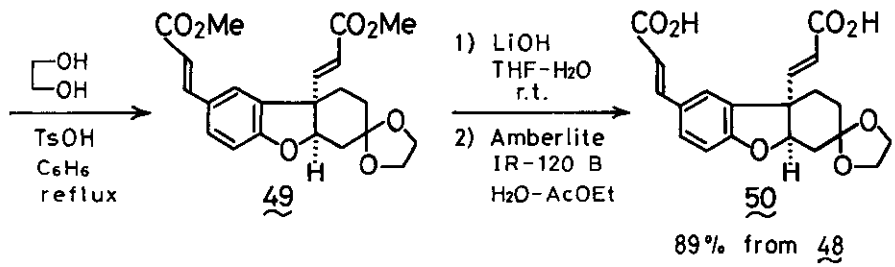
Subsequently we describe the first total synthesis of two natural alkaloids, lunarine (29) and lunaridine (30) as the racemates.[17]

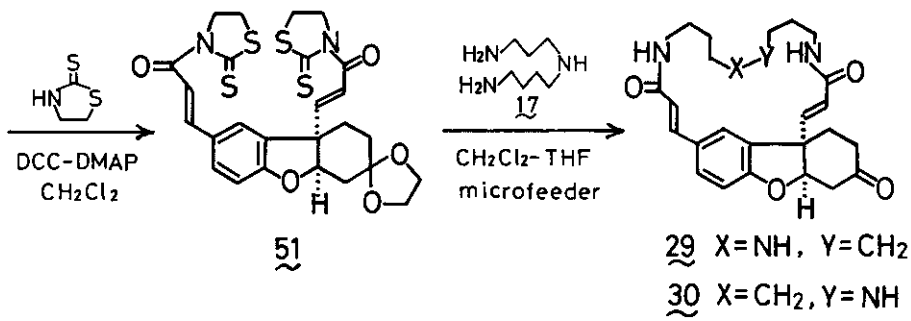
The pummerer ketone-like compound 44 was prepared from p-hydroxycinnamic acid (43) by the Potier's method.[22] Compound 44 on hydrogenation (H_2/Pd-C) gave the saturated keto-ester 45, which was protected as its ethylene acetal 46. The active methylenes of the molecule were sulfenylated by 2,2'-dipyridyl disulfide[23] to give an oily product 47. Oxidation of compound 47 to sulfoxide followed by heating in benzene afforded the transoid αβ-unsaturated ester 48 stereoselectively in 46% overall yield from 45. Its acetal 49 was hydrolized to yield the dicarboxylic acid 50 in 89% overall yield from 48. Compound 50 was converted into the key diamide 51 by the usual way. Aminolysis of this compound with spermidine (17) afforded a crude mixture of the desired alkaloids which was separated by the preparative t.l.c. to give pure (±)-lunarine (29) [Rf 0.6, mp>300° (from EtOH)] as colorless plates [18% overall yield from 50] and (±)-lunaridine (30) [Rf 0.2, decomp.>260° (from EtOH-acetone)] as a colorless solid [19.6% overall yield from 50]. The accomplishment of these total syntheses was confirmed by the identity of PMR data and retention times (HPLC) of the synthetic racemates, 29 and 30, with those of optically active natural lunarine and lunaridine, respectively.

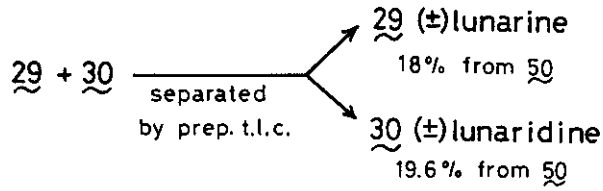

CO2H
OH
43
1) H2 / Pd-C
2) MeOH
conc. H2SO4
Δ 94%
CO2Me
OH
K3[Fe(CN)6]
Na2CO3
15%
CO2Me
CO2Me
O
H
44


H2 / Pd-C
67 %
CO2Me
CO2Me
O
H
45
OH
OH
TsOH
C6H6 reflux
46


1) LDA
2)
3) 10% HCl
4) NaHCO3
CO2Me
CO2Me
S
N
O
H
47
1) m-ClC6H4CO3H
2) C6H6
reflux
48
46% from 45


OH
OH
TsOH
C6H6
reflux
CO2Me
CO2Me
O
H
49
1) LiOH
THF-H2O
r.t.
2) Amberlite
IR-120 B
H2O-AcOEt
CO2H
CO2H
50
89% from 48


S
HN
S
DCC-DMAP
CH2Cl2
N
S
S
S
S
N
O
O
O
H
51
H2N
NH
H2N
17
CH2Cl2-THF
microfeeder
HN
X
Y
HN
O
O
O
H
29 X=NH, Y=CH2
30 X=CH2, Y=NH



Scheme 7

The cyclohexanone moiety was protected as the 1,3-dioxolan in the synthetic pathway from 48 to the diamide 51 in order to prevent the undesired side reaction to spiro compound 52 (Fig. 5).

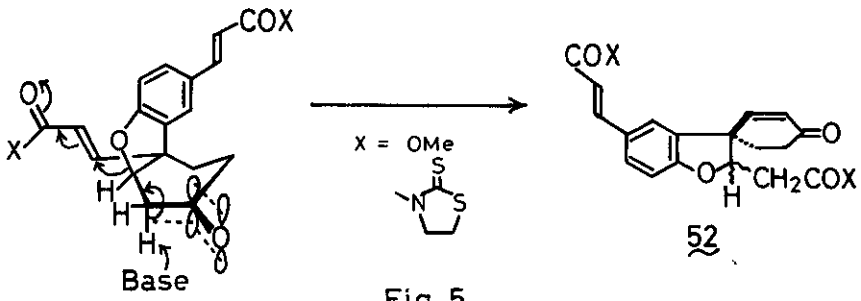


Fig. 5

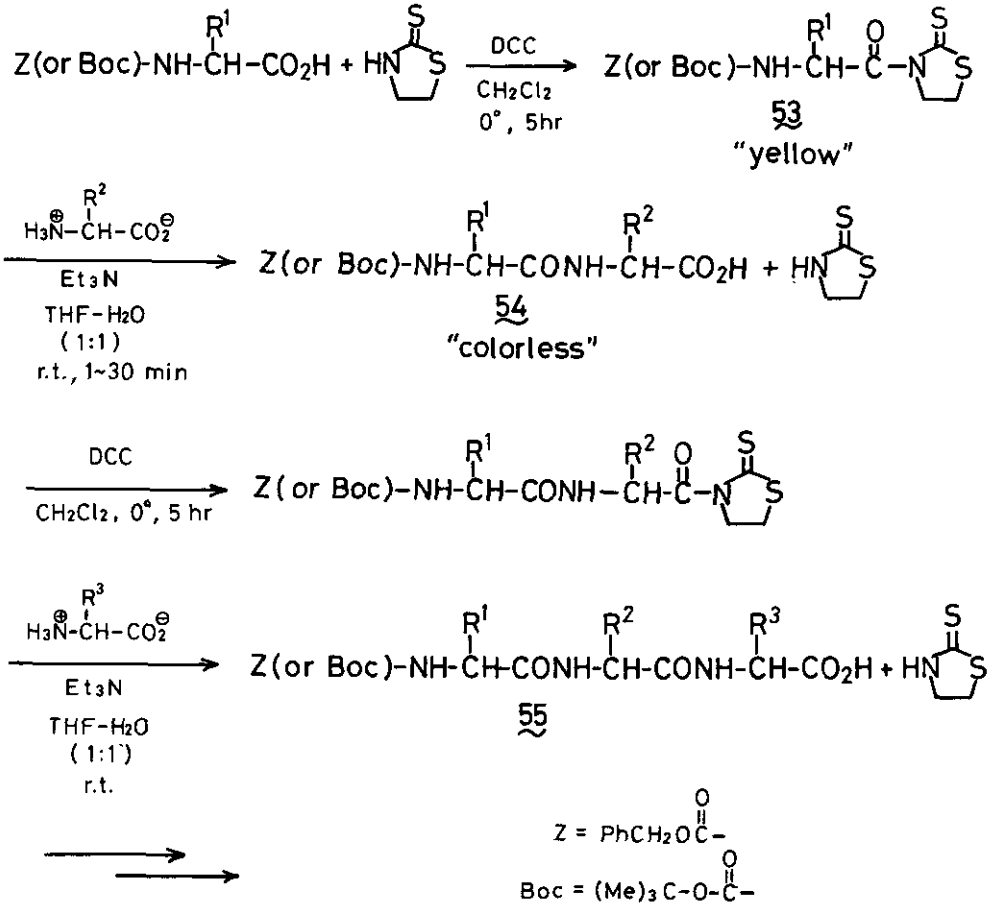
4. AMINOLYSIS OF ATT WITH AMINO ACID AND ITS DERIVATIVE[24]

As a new extention of the monitored aminolysis of ATT, we executed peptide bond formation, chemoselective acylation of amino acid, and bridging reaction of the enzyme model.

Monitored Peptide Bond Formation

We synthesized eight kinds of dipeptide and a tripeptide using this aminolysis. The accomplishment of the peptide bond formation can also easily be judged by the disappearance of the original yellow color due to ATT. There have been many reports on the condensing reagents for peptide bond formation, but such a nicely monitored method as ours has never been encountered. Synthetic sequence is illustrated in Scheme 8.

Preparation of four kinds of amino acid 1,3-thiazolidine-2-thione (TT) amides 53a~d is summarized in Table 1. Dipeptides 54a~h and tripeptide 55 were synthesized according to Scheme 8, which is summarized in Table 2.



Scheme 8

Table 1 1,3-Thiazolidine-2-thione Amide 53

amide	53	yield (%)	mp (°C)	$[\alpha]_D^{t°C}$	(t)
Z-L-Ala-R	53a	61	163-165°	-120.0°	(17)
Z-L-Met-R	53b	64	99-101	-97.2	(17)
Z-L-Leu-R	53c	83	78-79	-98.4	(21)
Boc-L-Phe-R	53d	77	168.5-170.5	-29.8	(19)

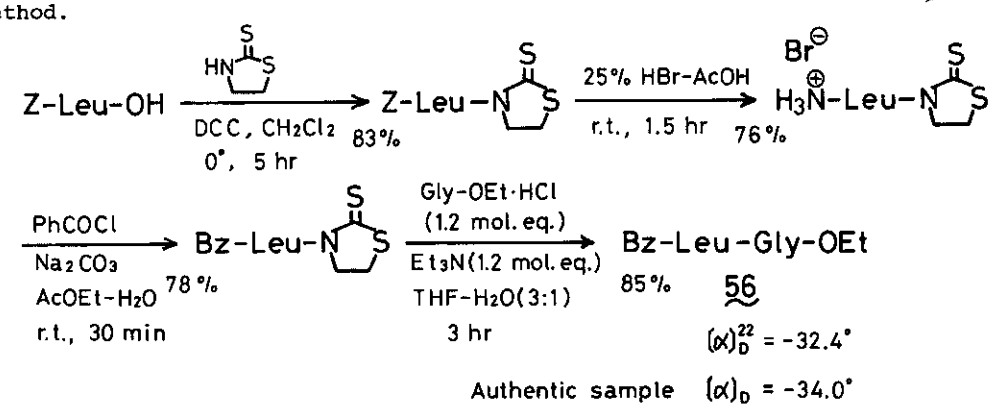
$[\alpha]_D$ in $CHCl_3$ (c = 2.0). R =

Table 2 Synthesis of Peptides 54 and 55

peptide 54 or 55		reaction time (min)	yield (%)	mp (°C)	$[\alpha]_D^{t°C}$	(c, solvent, t)
Z-L-Ala-Gly-OEt	54a	15	94	98-99	-19.7°	(1.0, EtOH, 23)
"	"	80*	94	99-100	-22.7	(1.1, EtOH, 17)
Z-L-Ala-Gly-OH	54b	1	89	128-129	-15.4	(0.91, EtOH, 23)
Z-L-Ala-L-Ser-OH	54c	30	88	194-196	+21.1	(0.4, DMF, 19)
Z-L-Ala-L-Thr-OH	54d	30	93	139-141	-8.2	(0.94, EtOH, 23)
Z-L-Met-Gly-OEt	54e	20	88	95.5-96.5	-17.0	(0.73, EtOH, 23)
"	"	110*	94	96-97	-19.6	(1.1, EtOH, 17)
Z-L-Ala-L-Phe-OH	54f	5	87	124-126	+39.2	(0.5, dioxane, 21)
Z-L-Met-L-Phe-OH	54g	20	95	125-126	+3.3	(1.0, EtOH, 19)
Boc-L-Phe-Gly-OH	54h	3	93	163-164	-5.5	(0.5, dioxane, 21)
Z-L-Leu-D-Ileu↓ L-(S-Bzyl)Cys-OH	55	120	87	132-135	-23.5	(2.0, DMF, 19)

* 1.1 Molar equiv. of Et_3N was employed. In other cases, 1.5-2.0 molar equiv. of Et_3N was used.

The Young test[25] of Bz-L-Leu-Gly-OEt (56), prepared according to Scheme 9, showed it to be 95% L-isomer in comparison with the same dipeptide derived from the azide method.

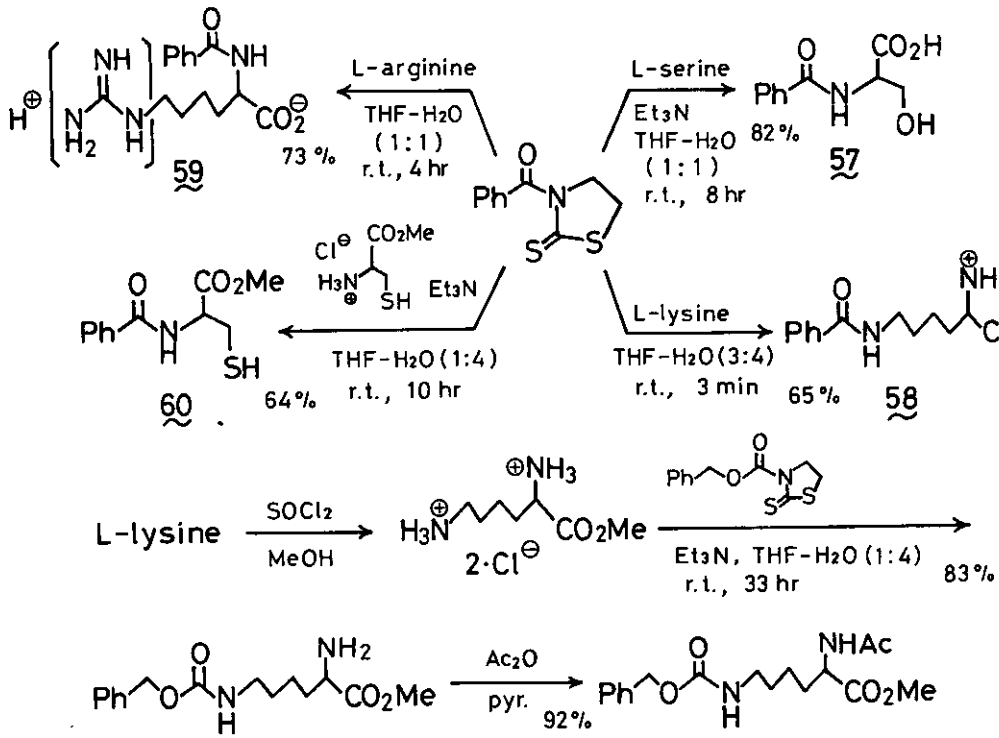


Scheme 9

This new monitored procedure may be very convenient because nonprotected amino acid is available and the released TT can be used recyclically.

Chemoselective Acylation

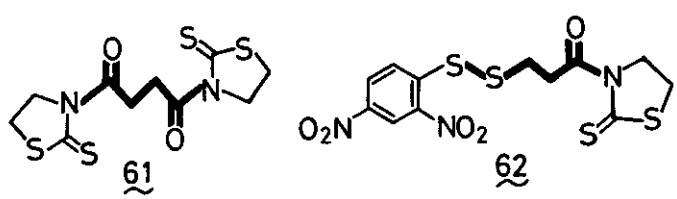
A chemoselective acylation of amino acid having three (or more) functional groups in the molecule, is very interesting from the viewpoints of peptide synthesis, chemical modification of enzyme, and synthesis of spermidine siderophore. Treatment of 3-benzoyl-TT with L-serine, L-lysine, L-arginine, and L-cysteine methyl ester resulted in a chemoselective formation of the corresponding benzoyl amides 57~60, respectively. Selective acylation of two types of amino groups in L-lysine was also carried out (Scheme 10).



Scheme 10

Bridging Reaction

Bridging in an enzyme or between enzymes by the particular reagent 61 or 62 having high reactivity to amino group or to amino and mercapto groups, respectively, is remarkably interesting in enzyme technology (see Fig. 6).



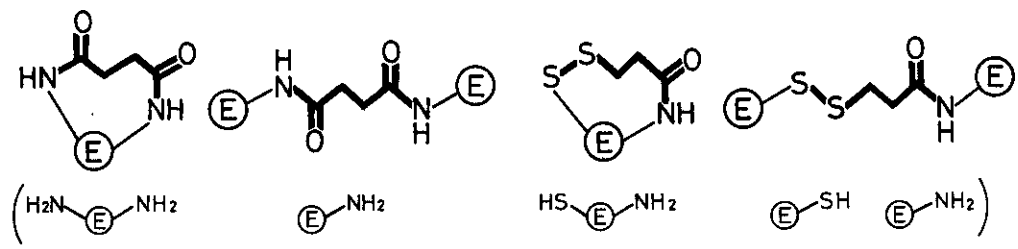
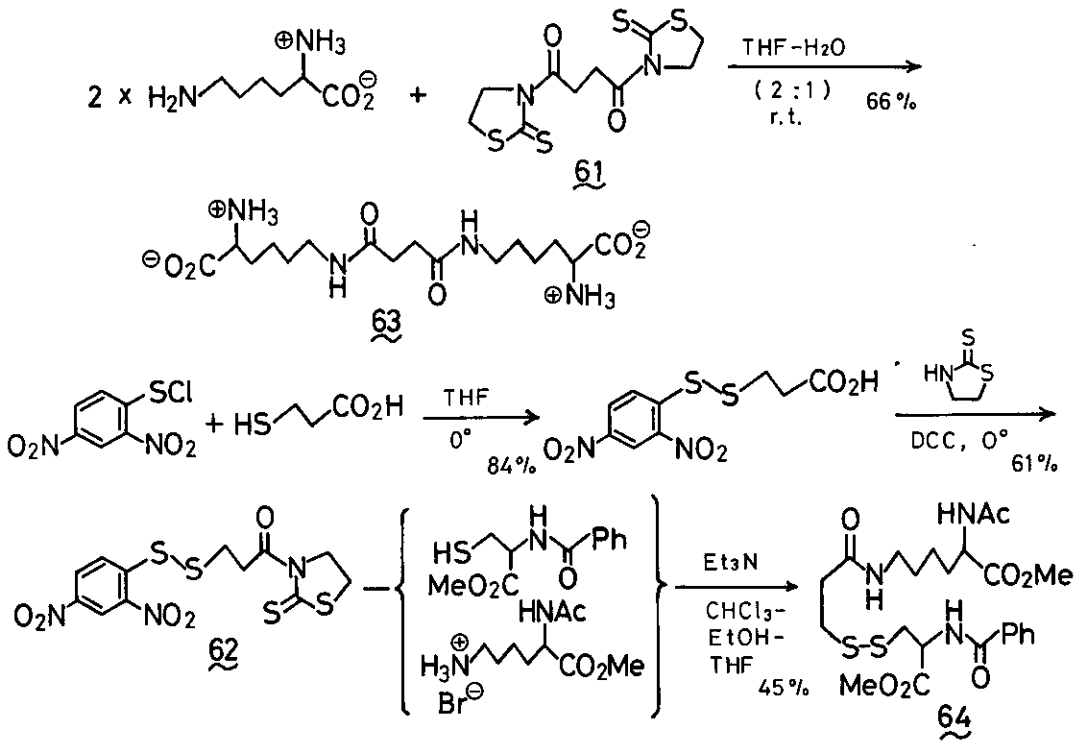


Fig. 6

As model experiments, the following two aminolyses were tried to give bridging products 63 and 64, respectively (Scheme 11).



Scheme 11

5. VERSATILITY OF ATT

ATT is highly reactive not only to several types of amino compounds but also to other nucleophiles (e. g. sodium borohydride,[26] di-isobutylaluminum hydride,[26] arylmagnesium bromide,[27] sodium alcoholate,[28] and sodium thiolate[28]) affording the corresponding products in high yield, as summarized in Fig. 7.

Reactions of ATT with some other nucleophiles, especially alkyl metal compounds, are being investigated.

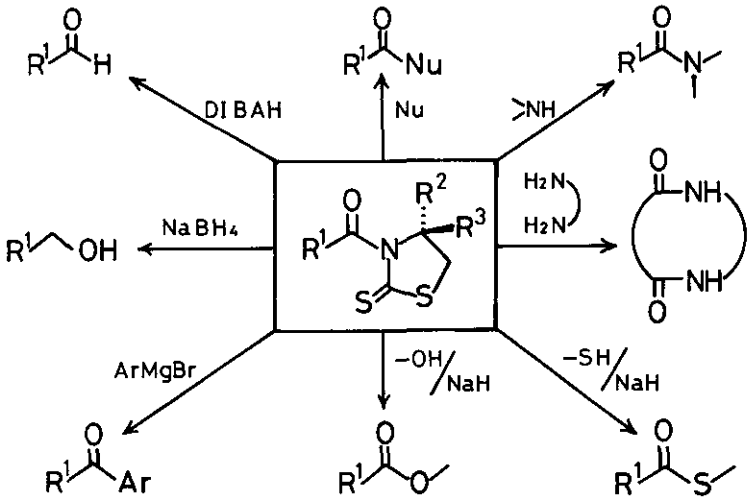
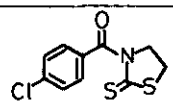
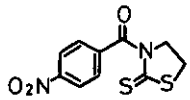
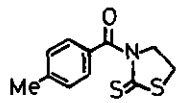


Fig.7

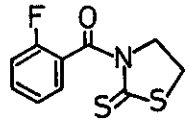
6. BIOLOGICAL AND PHYSIOLOGICAL ACTIVITIES OF ATT[29]

As a part of our projects, the screening tests for the biological and physiological activity were carried out on several ATT derivatives. ATT (1: R^1 = p-Cl-C_6H_5-, p-NO_2-C_6H_5-, p-Me-C_6H_5-) showed considerable activities against P 388 lymphocytic leukemia in mice (see Table 3). ATT (1: R = o-F-C_6H_5-) showed antitumor activity against Sarcoma 180 A ascites carcinoma innoculated into mice (see Fig. 8).

Table 3 Antitumor Activity against p 388 Lymphocytic Leukemia in Mice

compound	Dose (mg/kg)	T/C* (%)
	50	141
	100	141
	50	130
	100	142
	50	109
	100	135

* T/C (%) = (M.S.D. treated/M.S.D. control) x 100 Active ≥ 130%

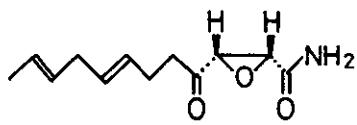


10 mg/kg T/C = 53 %
Active T/C ≦ 65 %

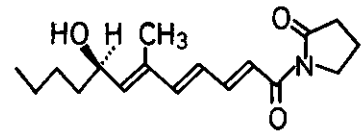
Fig. 8

ATT (1: R^1 = p-Cl-C_6H_5-, p-NO_2-C_6H_5-, C_6H_5-, $CH_3(CH_2)_{14}$-) also exhibited interesting fibrinolytic inducing activity.

An enzyme bridging reagent 62 showed inhibition activity to a fatty acid synthetase in Brevibacterium ammoniagenes. It activity (IC_{50} = 50 μg/ml) is lower than that (IC_{50} = 1 μg/ml) of cerulenin (65) but in almost the same grade as that (IC_{50} = 20 μg/ml) of variotin (66).



65



66

7. CONCLUSION

We have described mainly on the synthesis of macrocyclic spermidine alkaloids and peptides as an application of the new monitored aminolysis of ATT. During these studies, several ATT derivatives showed some interesting biological and/or physiological activities as we expected.

Thus it was demonstrated that ATT is not only the versatile chemical reagent but also a hopeful key-compound for drug-design.

In the future, we will hopefully extend the ATT chemistry to the field of asymmetric synthesis.

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