A NEW EFFICIENT AMINOLYSIS AND ITS APPLICATION TO SYNTHESIS OF MACROLACTAM ALKALOIDS

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Abstract— Aminolysis of 3-acylthiazolidine-2-thione has been shown to be an effective method for synthesis of amides. Applications of this procedure to syntheses of natural amide alkaloids and macrolactam alkaloids are described.
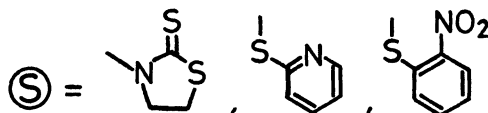
INTRODUCTION

New organic syntheses utilizing the sulfur-containing leaving groups have been recently exploited by our group. The mode of elimination of the sulfur-containing leaving group is classified into two types:
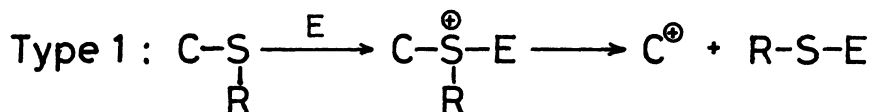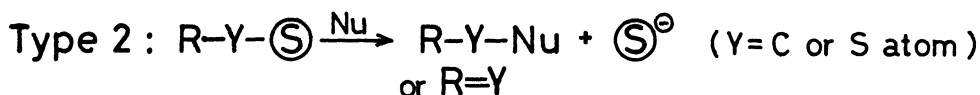
In the type 1 reaction, C-S bond cleavage is caused with the assistance of an electrophilic thiophile, while in the type 2 reaction Y-Ⓢ bond cleavage is facilitated by the sulfur-containing active leaving group Ⓢ.

In this acount, I wish to outline a type 2 reaction in which 3-acyl-thiazolidine-2-thione is used as R-Y-Ⓢ and an amine as the nucleophile.

MONITORED AMINOLYSIS——SYNTHESIS OF AMIDE

First, our attention was directed to a yellow product formed from the reaction of thiazolidine-2-thione thallium(I) salt (1) (Ref. 1) with carboxylic acid chloride. The compound, to which the thioester structure 2 was incorrectly assigned by us, was treated with di-isobutylaluminum hydride (DIBAH) or sodium borohydride. Completion of the reaction was easily judged

by the disappearance of the original yellow color, and aldehyde or alcohol
was obtained in high yield, respectively (Ref. 2). At almost the same time,
Izawa and Mukaiyama reported the reduction of amide 3 into aldehyde by
DIBAH (Ref. 3). Two compounds, prepared in our laboratory by the reactions
of 1 with p-bromobenzoyl chloride and of 1 with adipoyl dichloride, were
subjected to the X-ray crystallographic analysis. Their structures were
shown to be 4 and 5, respectively (Ref. 4 and 5). Thus the work carried out
independently by Mukaiyama's group and ours proved to be the same, and we
revised the thioester structure to the amide structure (Ref. 6).

Thereafter, the structures of several products prepared from the reactions
of 1 with acyl halides or β-oxo halides were checked by ^{13}C NMR spectra.
The thiazolidine-2-thione amide derivatives were shown to exhibit a
characteristic signal due to $>^{13}$C=S at ca. 200 ppm, while the 2-thiazoline-
2-thiol ether derivatives showed a signal due to $>^{13}$C=N— at ca. 164 ppm.
The products from the reactions with acyl halides were shown to be amides 3,
while those from the reactions with β-oxo halides were thioethers 6. Thus
compound 1 has an ambident nature, which differs from 7 and 8.
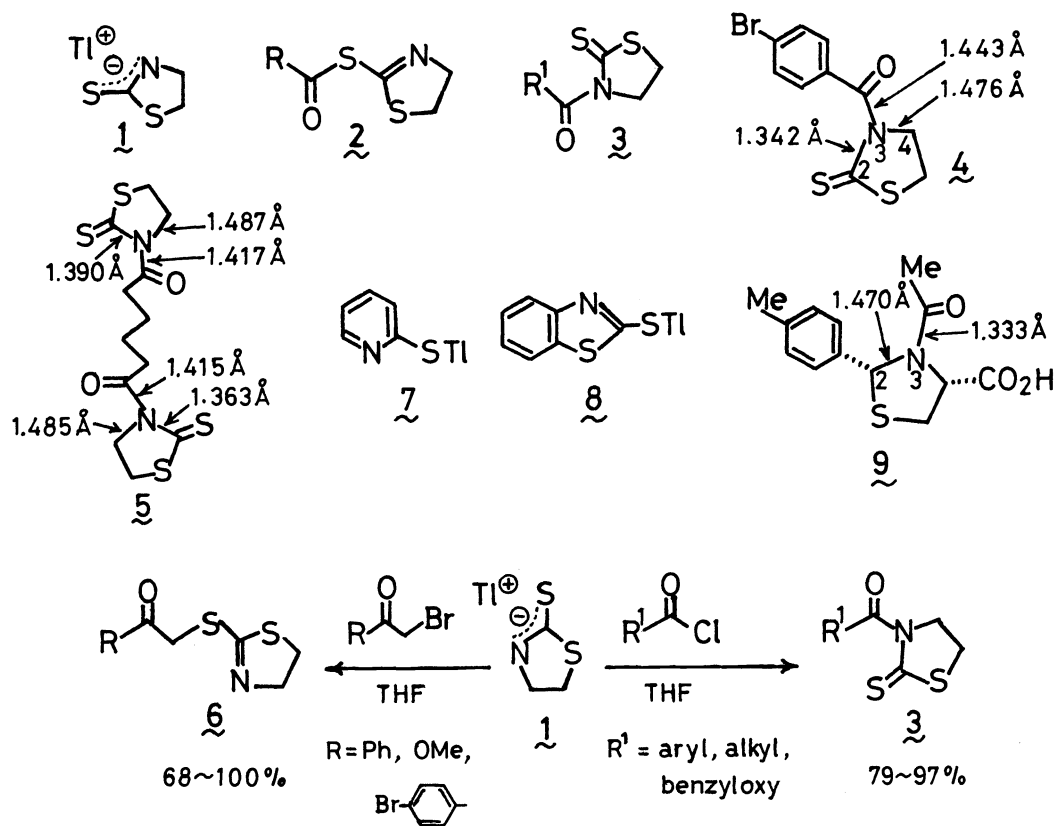
The rationalized explanation is: the reaction from 1 to 6 is controlled by
the "Soft-Soft specific affinity", while the reaction from 1 to 3 is
controlled by the "Hard-Hard specific affinity"(Ref. 7).

As shown in the formulas, X-ray analysis showed that both compounds 4 and 5 had
a longer amide C-N bond than that of the usual amide 9 (Ref. 8), while both
had the shorter C(2)-N(3) bond than their N(3)-C(4) bond and the C(2)-N(3)

bond in 9. This means that the lone pair on the amide nitrogen atom in the
compounds 4 and 5 conjugates with the thiocarbonyl group rather than the
carbonyl group.   Although the foregoing product was unexpectedly not thio-
ester 2 but amide 3, its carbonyl group was found to be activated
satisfactorily.   The amide 3 could also be synthesized in good yield by a
condensation of carboxylic acid with thiazolidine-2-thione in the presence
of dicyclohexylcarbodiimide (DCC).
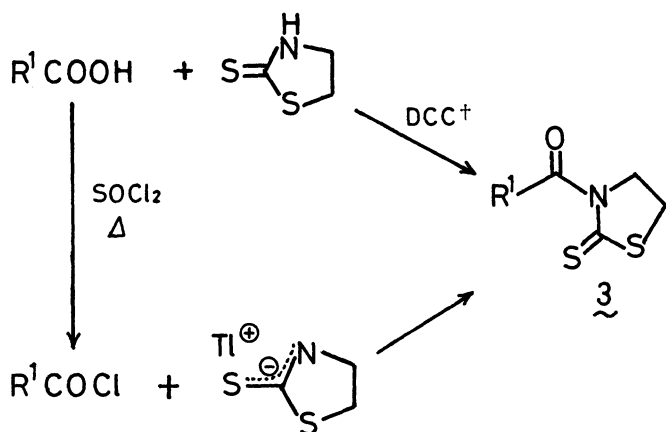
† Sometimes, addition
of a catalytic
amount of 4-dimethyl-
aminopyridine (DMAP)
increases the reac-
tion rate.

3-Acylthiazolidine-2-thione 3 on treatment with amines under mild conditions
gave amide in high yield through aminolysis (Ref. 9).   This reaction could
also be monitored by the disappearance of the original yellow color of the
starting material.
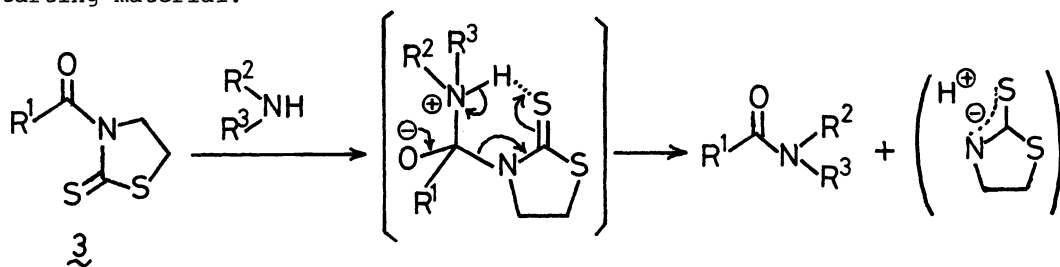
R^1 = C_8H_{17}, $C_{15}H_{31}$, Ph, $PhCH_2$, $PhCH_2O$, PhCH=CH-, p-$MeOC_6H_4CO(CH_2)_2$-;

R^2 = alkyl, aryl; R^3 = alkyl, H; or R^2 = R^3 = -$(CH_2)_n$- (n = 4, 5, 6)

In an example of the actual experimental method with 3-hexadecanoylthiazol-
idine-2-thione 3 (R^1 = $C_{15}H_{31}$), a solution of amine (1.1 mol equiv.) in di-
chloromethane was added dropwise to a solution of 3 (1.0 mol equiv.) in di-
chloromethane with stirring.   When the yellow color of the reaction mixture
disappeared, the reaction ended, and the solvent was evaporated in vacuo.
The residue left was chromatographed on a silica gel column impregnated by
10% of silver nitrate to remove thiazolidine-2-thione by adsorption.   The
desired amide was thus obtained in high yield.

The results of aminolysis of the same compound 3 (R^1 = $C_{15}H_{31}$) with several

amines are summarized in Table 1.

TABLE 1.   Aminolysis of 3-hexadecanoylthiazolidine-2-thione.

Amine: R^2-NH-R^3		Reaction time	Yield(%) of $C_{15}H_{31}CONR^2R^3$
R^2	R^3		
n-Bu	H	1 min	96
sec-Bu	H	30 min	97
tert-Bu	H	70 hr	98
cyclohexyl	H	5 min	92
benzyl	H	95 hr	91
phenyl	H	150 hr	93
n-Bu	CH_3	5 min	98
n-Bu	n-Bu	15 min	99
cyclohexyl	CH_3	10 min	99
benzyl	CH_3	8 min	95
-$(CH_2)_4$-		1 min	98
-$(CH_2)_5$-		1 min	99
-$(CH_2)_6$-		1 min	99
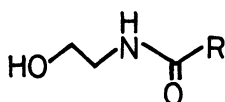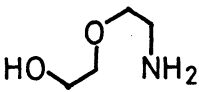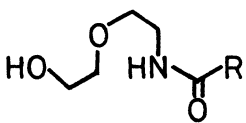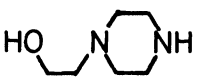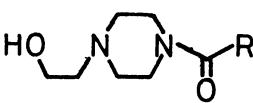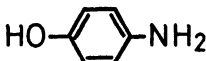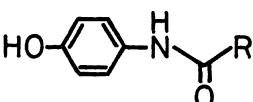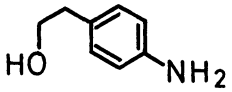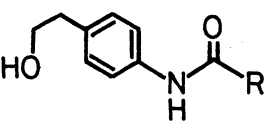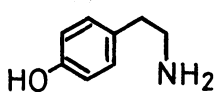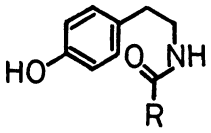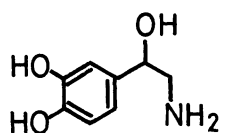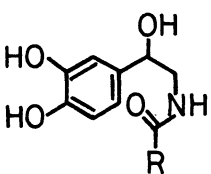
The rate of this aminolysis depends upon the electron density on the nitrogen atom of the amine and its steric surroundings. Comparison of the reaction rate observed in terms of amines gave: aliphatic amine > aromatic amine; RCH_2NH_2 > R_2CHNH_2 ≫ R_3CNH; RNH_2 ≥ $RR'NH$; $(CH_2)_n NH$ (n = 4-6) > R_2NH.

Aminolysis of various R^1 derivatives of 3 with several amines proceeded also very smoothly and was finished generally within a short time. Thus, amides 10-15 were obtained in high yield as shown below. We found that only the amides of the primary amines, i.e., 16, 17, and 23, were selectively formed on the aminolysis with such a diamine as tryptamine or such triamines as histamine and spermidine (22).

10   97%   11   98%   12   98%   13   100%

14   94%   15   98%   16   93%   17   98%
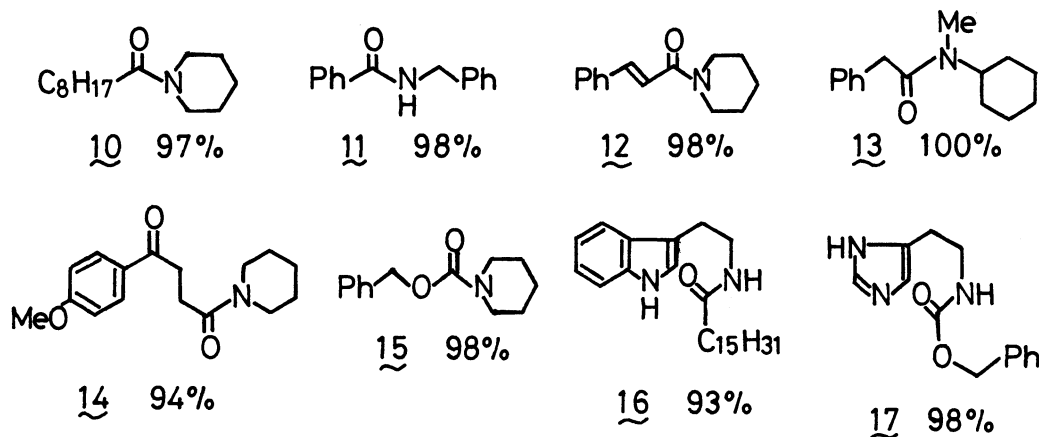
The amide 3 (R^1 = C$_{15}$H$_{31}$) on treatment with aminoalcohols or aminophenols chemoselectively gave only the amides having free hydroxyl group(s). The results are shown in Table 2.

TABLE 2. Aminolysis of 3-hexadecanoylthiazolidine-2-thione with aminoalcohol or aminophenol.

| Aminoalcohol Aminophenol	Solvent	Reaction time	Product (R = C$_{15}$H$_{31}$)	Yield %
HO–CH$_2$CH$_2$–NH$_2$ (2-aminoethanol)	CH$_2$Cl$_2$	20 min	HO–CH$_2$CH$_2$–NH–C(=O)–R	91
HO–CH$_2$CH$_2$–O–CH$_2$CH$_2$–NH$_2$	CH$_2$Cl$_2$	30 min	HO–CH$_2$CH$_2$–O–CH$_2$CH$_2$–NH–C(=O)–R	75
HO–CH$_2$CH$_2$–N(piperazine)NH	CH$_2$Cl$_2$	3 min	HO–CH$_2$CH$_2$–N(piperazine)N–C(=O)–R	95
HO–C$_6$H$_4$–NH$_2$	THF	7 days	HO–C$_6$H$_4$–NH–C(=O)–R	63
HO–CH$_2$–C$_6$H$_4$–NH$_2$	THF	7 days	HO–CH$_2$–C$_6$H$_4$–NH–C(=O)–R	61
HO–C$_6$H$_4$–CH$_2$CH$_2$–NH$_2$	EtOH–THF	3 min	HO–C$_6$H$_4$–CH$_2$CH$_2$–NH–C(=O)–R	95
(HO)$_2$C$_6$H$_3$–CH(OH)–CH$_2$–NH$_2$	EtOH–THF	5 hr	(HO)$_2$C$_6$H$_3$–CH(OH)–CH$_2$–NH–C(=O)–R	51

It is advantageous that this reaction can be carried out without protection of the hydroxyl group and even in ethanol. Thus, N-hexadecanoylation of glucosamine hydrochloride (18) was tried in sulfolane in the presence of triethylamine to give a 74% of amide 19 (Ref. 9).

Another example of selective N-acylation was shown by the reaction with L-serine. This reaction was successfully carried out in aqueous tetrahydrofuran solution (Ref. 10).

This aminolysis was used in the synthesis of the natural amide alkaloids,
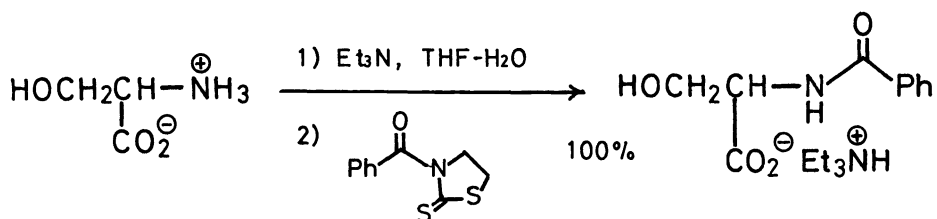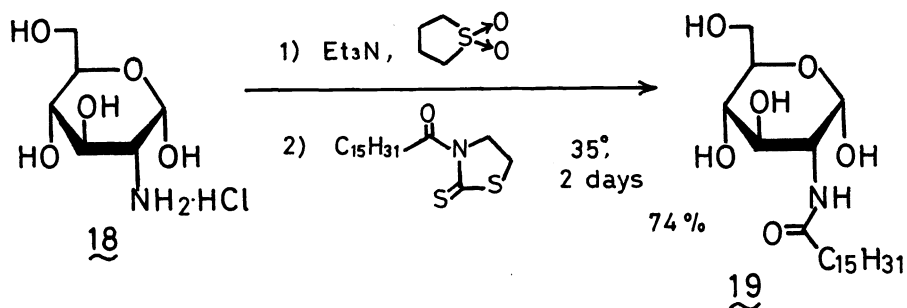
fagaramide (20) isolated from Fagara macrophylla (Ref. 11), dolichotheline
(21) from Dolichothele sphaerica (Ref. 12), maytenine (23) from Maytenus
chuchuhuasha (Ref. 13), and N-ferulyltryptamine (24), a very minor component
of Zea mays (Ref. 14).
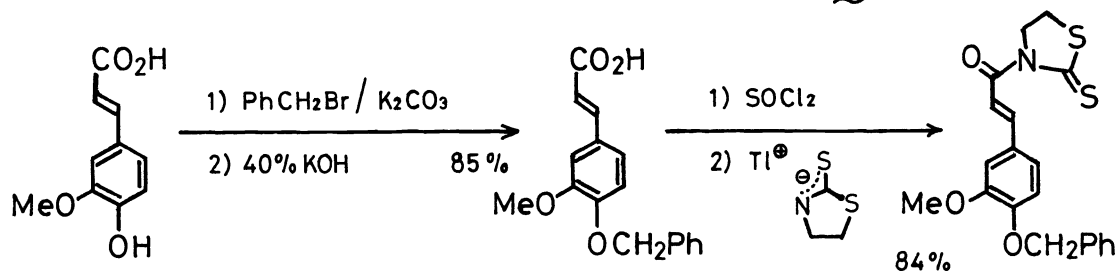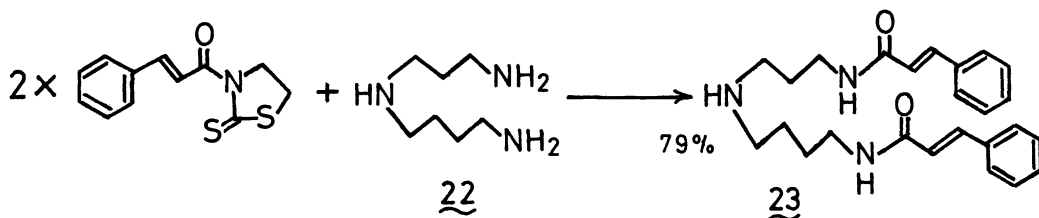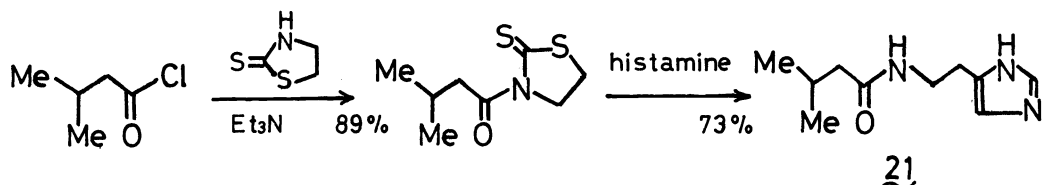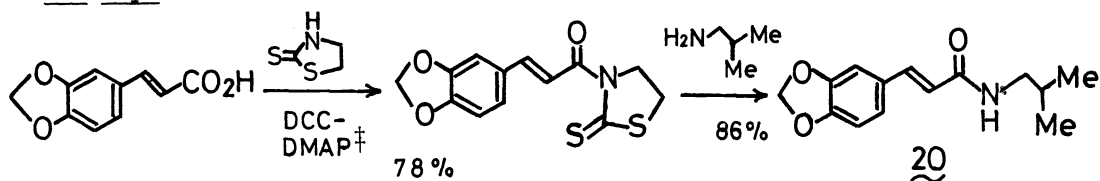
‡ Addition of a catalytic amount of 4-dimethylaminopyridine made the
  reaction rate much faster (Ref. 15).

SYNRHESIS OF MACROLACTAMS

We have been interested in the biologically active polyamines (e.g., spermidine, homospermidine, spermine, etc.) and their derivatives and in the macrolactam alkaloids containing these polyamines as part of th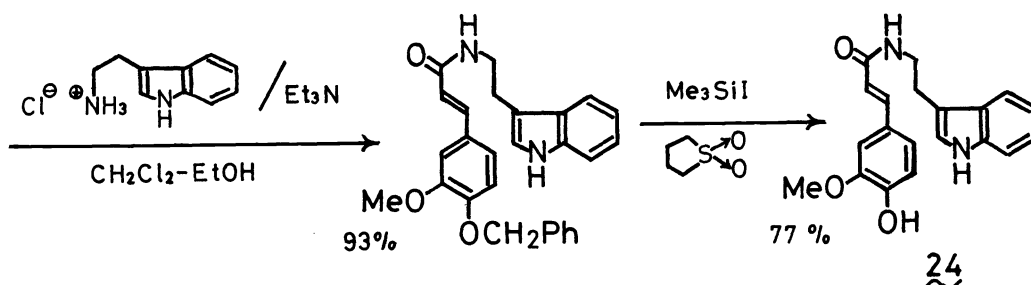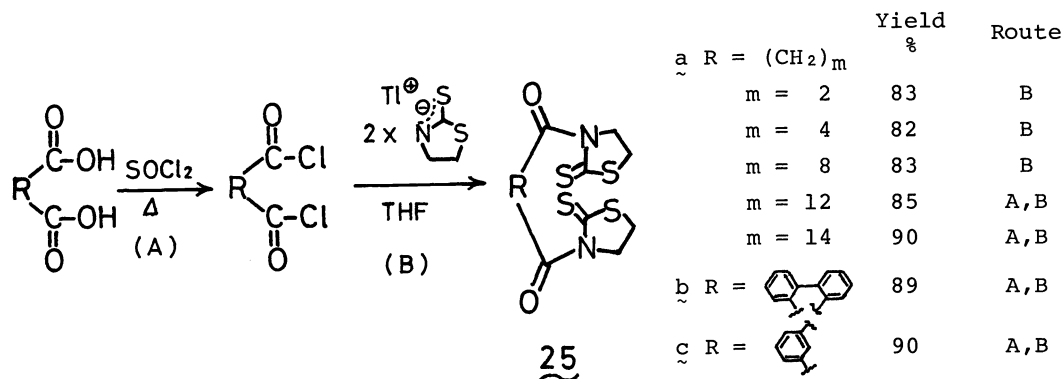eir structure. Application of aminolysis of 3-acylthiazolidine-2-thione (3) to synthesis of macrolactams was thus attempted. The diamides of dicarboxylic acids with thiazolidine-2-thione were prepared through the following route:

			Yield %	Route
a R = $(CH_2)_m$				
	m =	2	83	B
	m =	4	82	B
	m =	8	83	B
	m =	12	85	A,B
	m =	14	90	A,B
b R =			89	A,B
c R =			90	A,B

Subsequent macrolactam ring formation was performed by the high dilution method. A yellow solution of 25a (0.80 mmol) in dichloromethane (20 ml) and a solution of diamine 26 (0.96 mmol) in dichloromethane (20 ml) were added dropwise using two mechanically driven syringes over two hours into dichloromethane (130 ml) under nitrogen with stirring at room temperature. After evaporation of the colorless solution in vacuo, the residue was chromatographed on a column prepared from Sephadex LH-20 and methanol to separate the macrocyclic diamide 27 and/or tetramide 28 in good yield.

A similar reaction took place also between 25a (m = 8 and 12) and spermidine (22) and gave a good yield of the desirable macrocyclic diamides 29a,b, in which the secondary amine remained intact. These findings were useful for the synthesis of lunarine (37) (20-membered ring) and codonocarpine (32) (24-membered ring).

The results obtained from the experiments described above are summarized in Table 3 (Ref. 16).
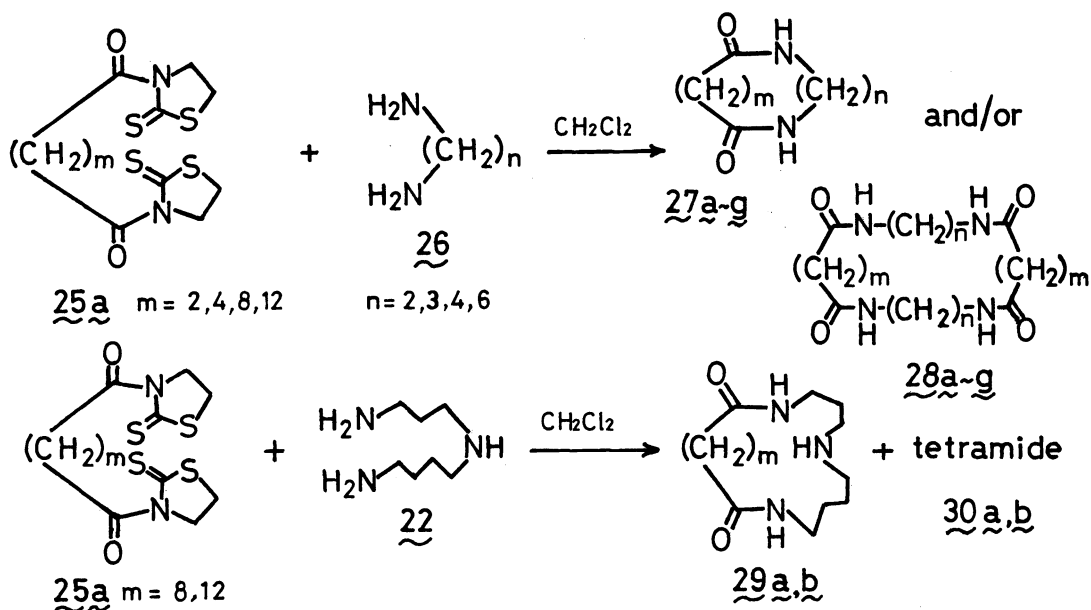
$(CH_2)_m$ 25a   m = 2,4,8,12   + H_2N $(CH_2)_n$ H_2N 26   n = 2,3,4,6 $\xrightarrow{CH_2Cl_2}$ 27a~g   and/or   28a~g   + tetramide

$(CH_2)_m$ 25a   m = 8,12   + H_2N — H_2N — NH   22 $\xrightarrow{CH_2Cl_2}$ 29a,b   + tetramide   30a,b

TABLE 3. Synthesis of macrocyclic diamide and tetramide.

25a m	Diamine 26 Spermidine (22)	Macrocyclic diamide [Ring size]	Yield %	Macrocyclic tetramide [Ring size]	yield %
2	26: n = 2	27a [8]		28a [16]	84
2	26: n = 3	27b [9]		28b [18]	82
4	26: n = 3	27c [11]		28c [22]	89
4	26: n = 4	27d [12]		28d [24]	80
4	26: n = 6	27e [14]	34	28e [28]	37
8	26: n = 6	27f [18]	66	28f [36]	12
12	26: n = 6	27g [22]	83	28g [44]	8
8	22	29a [20]	89	30a [40]	
12	22	29b [24]	85	30b [48]	5

An alternative synthesis of macrocyclic diamide 29a was tried by the drop-
wise addition of a solution of spermidine (22) (0.96 mmol) in dichloro-
methane (20 ml) into a solution of 25a(m = 8) (0.80 mmol) in dichloromethane
(150 ml) with stirring over two hours. In this case also, a high yield
(83%) of diamide 29a was obtained. Surprisingly, the secondary amino group
of product 29a formed at the early stage of the aminolysis did not react
with a large excess of 25a(m = 8). This is probably due to a decrease in
the nucleophilicity of its secondary amino group, caused by a stable six-
membered hydrogen bond formation between the lone pair on the secondary
amine and an amide hydrogen in the molecule (see formula 31). The same
effect can also be expected in the spermidine (22) molecule. This
information was useful for synthesis of the spermidine alkaloids.

Subsequently, we tried the reaction between 25a(m = 12) and 26(n = 2), i.e.,

31
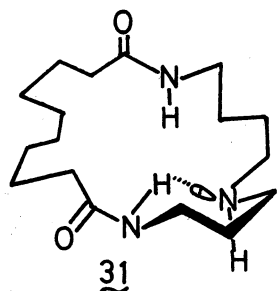
between the reactants having the extreme-
ly different carbon chain lengths (m≫n);
the 18-membered cyclic diamide and the
36-membered ring tetramide were obtained
in 69% and 18% yields. Another example
is shown by the reaction between 25a
(m = 14) and 26 (n = 4) (Ref. 17).

25a m=12   + **26** n = 2   ⟶   **18** 69%   +   **36** 18%

25a m=14   + **26** n = 4   ⟶   **22** 64%   +   **44** 17%
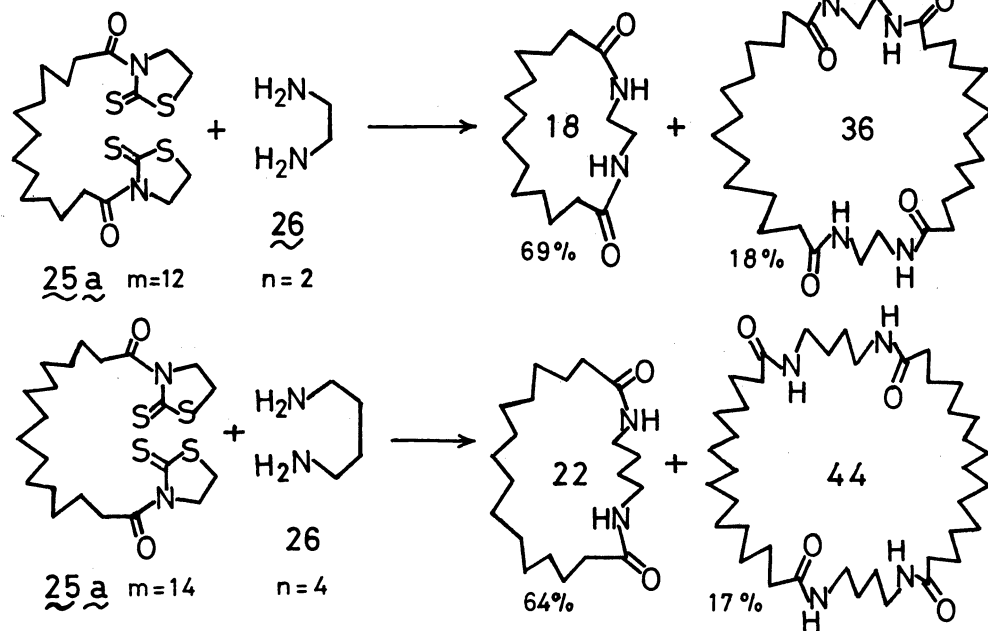
The results shown in Table 3 suggested that macrolactam ring formation is
controlled by the strain in the cyclization transition state. The 8-12-
membered ring diamides have not been obtained (Ref. 18).

Further applications of this aminolysis to macrolactam syntheses are shown
by the structures and yields of the following products:

R = —(CH₂)₁₂—   95%

= —(CH₂)₁₄—   79%

=   91%

=   50%

93%

79%

76%
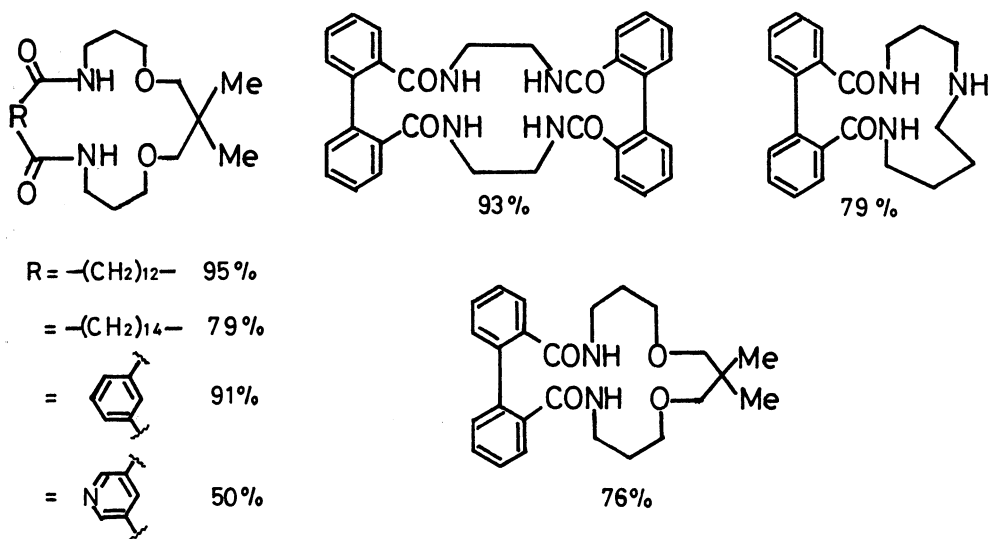
These compounds may have some utility for metal complex formation (Ref. 19) or, in the case of the pyridine derivative, as an NAD model (Ref. 20).

TOTAL SYNTHESIS OF MACROCYCLIC SPERMIDINE ALKALOIDS

Total synthesis of spermidine alkaloids using the foregoing aminolysis was attempted. The first target was codonocarpine (33) isolated from Codono-carpus australis by Doskotch and his coworkers (Ref. 21). Diamide 32 was synthesized and subjected to the reaction with spermidine (22) to give a mixture of codonocarpine (33) and its isomer 34, which was separated by droplet counter-current chromatography (DCCC) (Ref. 22). The sequence of the synthesis was:
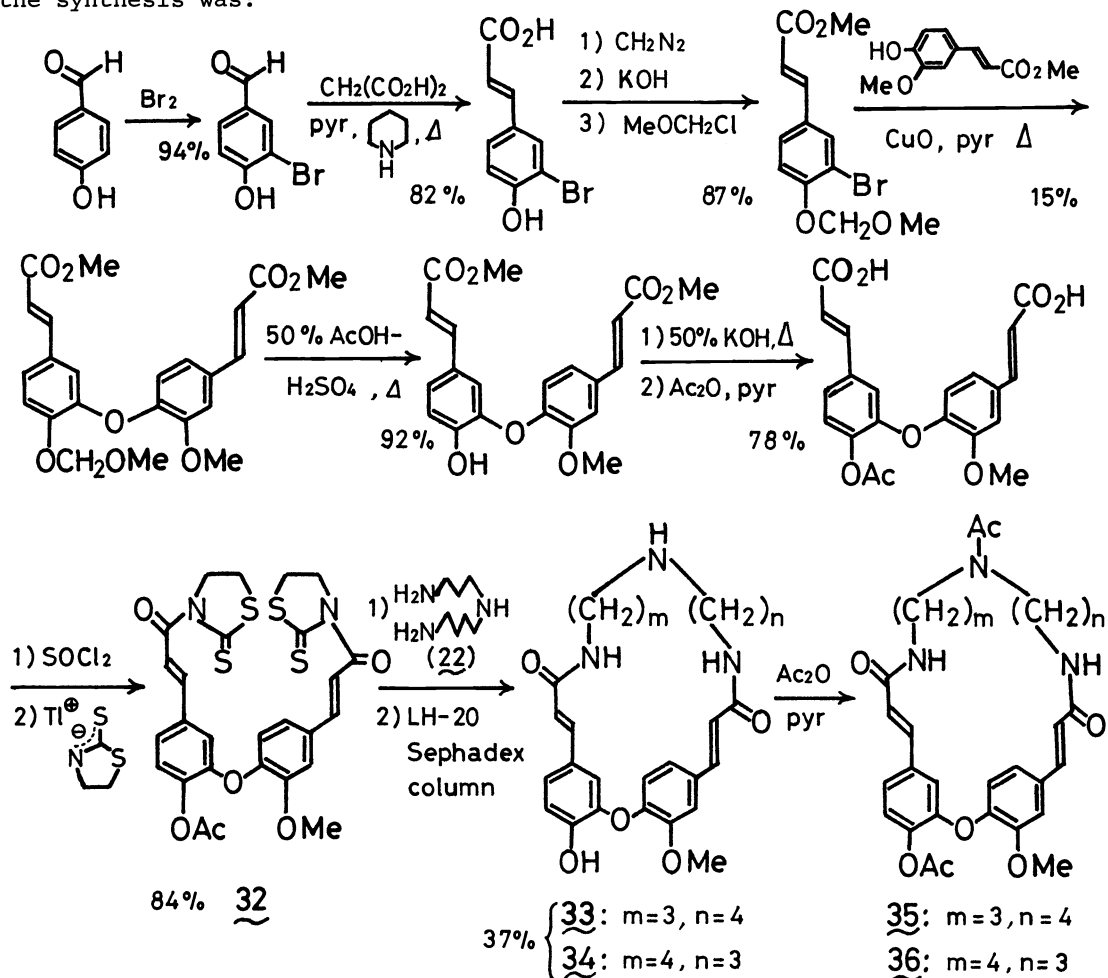

The accomplishment of this total synthesis was confirmed by the melting point of the pale yellow prisms of codonocarpine (33), mp 183-187° [lit. (Ref. 21): mp 187°], and its spectral data which were identical with those reported for the natural alkaloid. Further confirmation of this total synthesis came from the mixed melting point of N,O-diacetylcodonocarpine (35) with an authentic sample and also from the identical spectra of 35 and the authentic sample. In addition, the isomer 34 was obtained as yellowish prisms of mp 243-246° (decomp.) and its spectroscopic data agreed with the structure assigned.

The second targets were lunarine (42) and lunaridine (43), which were
isolated from Lunaria biennis by Potier and his coworkers (Ref. 23). As a
model experiment, a mixture of their racemic tetrahydro-derivatives was
successfully synthesized as outlined below:
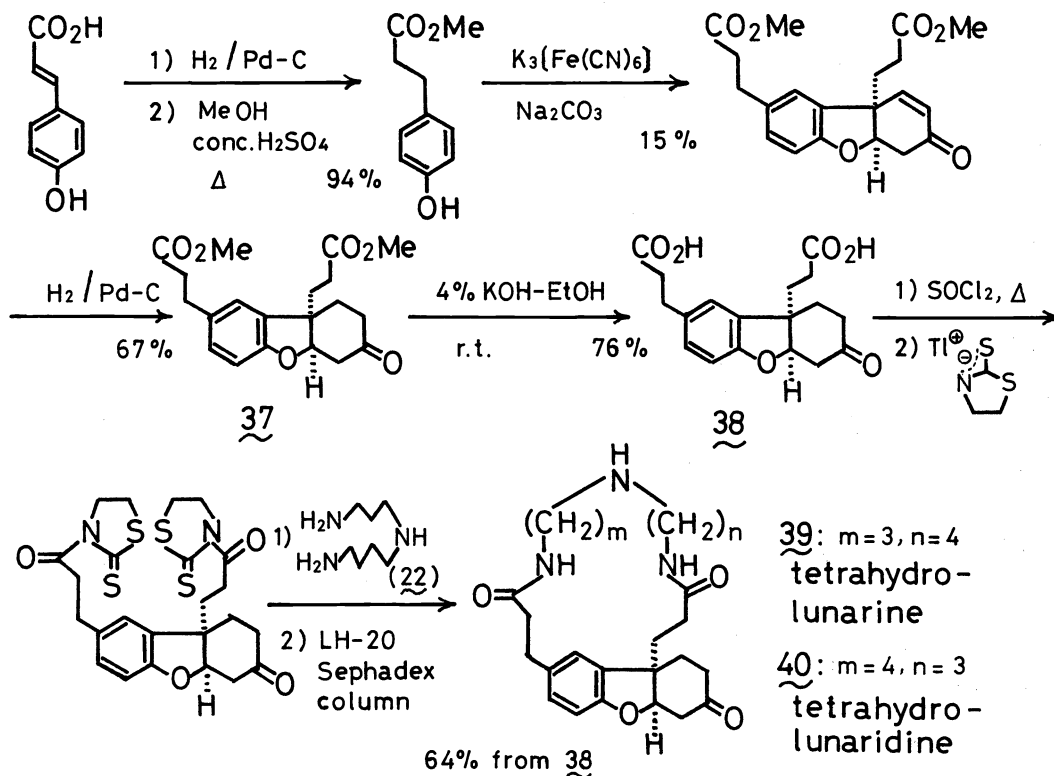
Next, an approach to the synthesis of the racemates of both natural alkal-
oids was tried as shown below. The key reaction of diamide 41 with
spermidine (22) is now being studied.

41   (22)   **42** : m=3 n=4
   **43** : m=4, n=3
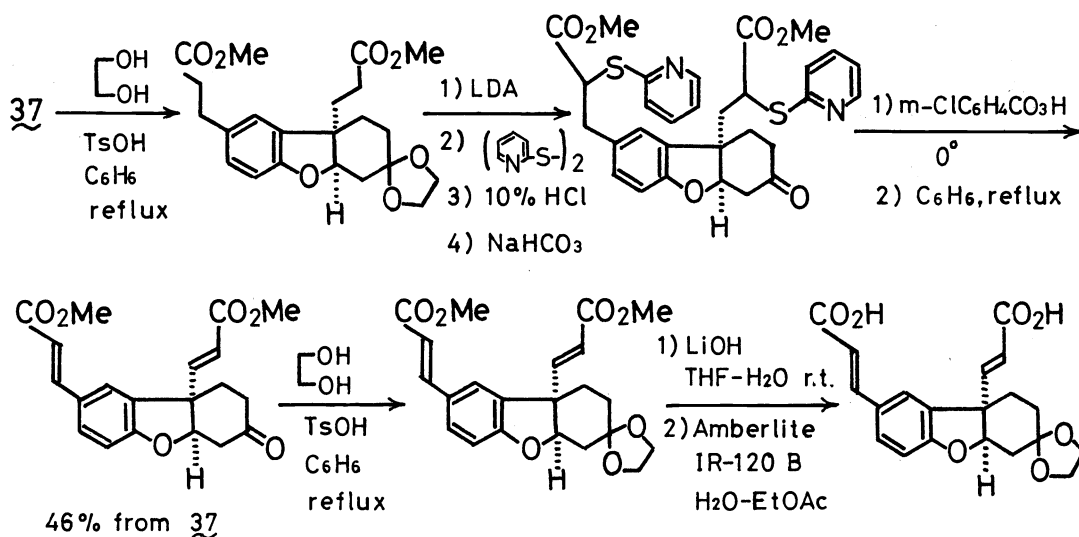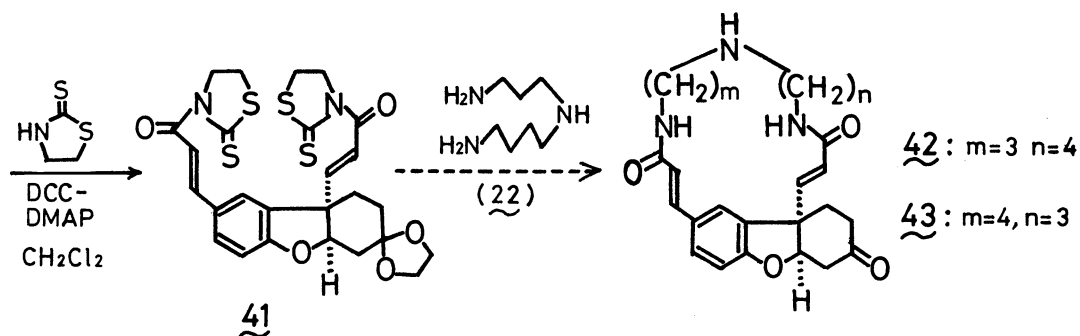
REACTIVITY OF 3-ACYLTHIAZOLIDINE-2-THIONE AND ITS BIOLOGICAL ACTIVITY

The structure of 3-acylthiazolidine-2-thione is similar to that of
penicillin. The biological activity of penicillin is based upon enzymatic
attack by penicillin-sensitive bacteria on the β-lactam ring. The aminolysis
of 3-acylthiazolidine-2-thione may be regarded as a similar type reaction.
This suggests, therefore, that these compounds may exhibit similar biological
activity (see the formulas).

penicillin   3-acylthiazolidine-
                         2-thione
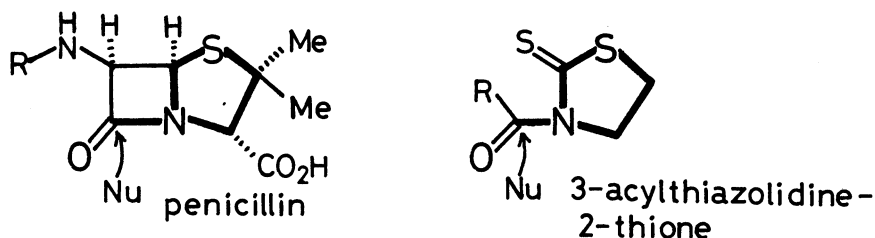
Although the results for their antibiotic activity test have not been
available, some derivatives of this type compound have been proved to have
antitumor activity to the P388 lymphocytic leukemia in mice (Ref. 24).
However, 3-acylthiazolidine-2-thione did not react with adenosine or cytidine
(as the nucleic acid models). In contrast, the reaction of 3-benzoyl-
thiazolidine-2-thione with L-lysine or L-arginine (as the enzyme models)
proceeded smoothly, and the amino acids were effectively converted into
their ω-N-benzoyl derivatives.

87%
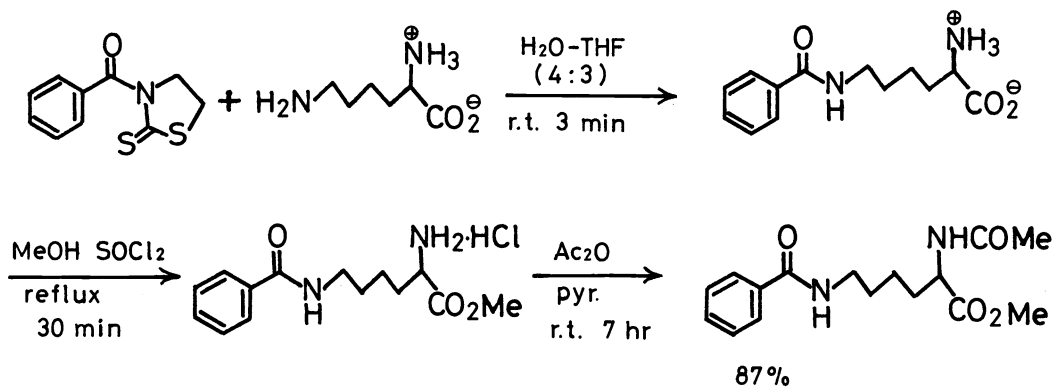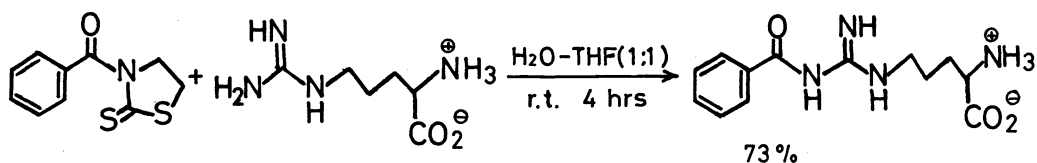
These results suggest that their antitumor activity may be attributed to the irreversible inactivation based on acylation of the amino groups in some specific enzymes in the tumor cells by this type of compound.

CONCLUSION

Our new aminolysis has thus been shown to be very useful method for the synthesis of amides. The 2-thiocarbonylthiazolidino group was demonstrated to be an excellent leaving group with a wide variety of synthetic uses. Other uses of 3-acylthiazolidine-2-thione will be explored in the future, for instance, in peptide synthesis, in new carbon-carbon formation methods, in asymmetric synthesis, and in development of new biologically active derivatives.

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ADDENDA

A short communication of the total synthesis of codonocarpine (33) is in
press on Tetrahedron Letters.

Soon after submitting this manuscript, the total synthesis of dl-lunarine (42)
and dl-lunaridine (43) was also accomplished.