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## ALPHA-OXIDATION OF AMINE DERIVATIVES BY BIS(2,2,2-TRICHLOROETHYL) AZODICARBOXYLATE AND APPLICATION OF ITS PRODUCTS AS IMINIUM ION EQUIVALENTS

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This paper is dedicated to the celebration of the Prof. Dr. Masakatsu Shibasaki 70th birthday.

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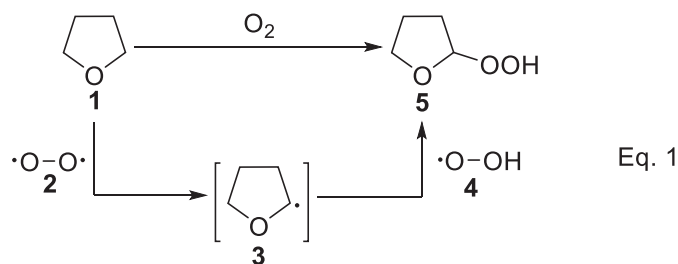
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**Abstract** – Alpha-oxidation of amine derivatives by azodicarboxylate was examined. Among several azodicarboxylate esters and amides tested, bis(2,2,2-trichloroethyl) azodicarboxylate, that has highly electrophilic 2,2,2-trichloroethoxycarbonyl functional groups, was found to have excellent oxidation reactivity. Acylated or carbamoylated amines were suitable substrates for this reaction condition. Tertiary amines could react in the same manner, but spontaneous elimination of hydrazinyl group occurred to give dimerized products. The reaction products were found to react with nucleophiles in the presence of Lewis or Brønsted acid catalyst. This strongly suggests that the reaction products, alpha-hydrazinated amine derivatives, might serve as carbonyl group equivalents, very useful intermediates in synthetic organic chemistry.

## INTRODUCTION

It is well-known that ethers such as THF and diethyl ether often lead to formation of peroxides under aerial atmosphere. For example, when THF **1** is exposed to the air for a long time of period, **1** is often oxidized to peroxide **5**. In this reaction, oxygen molecule **2** is inserted into C-H bond at alpha position of oxygen atom of **1** (Eq. 1).<sup>1</sup>

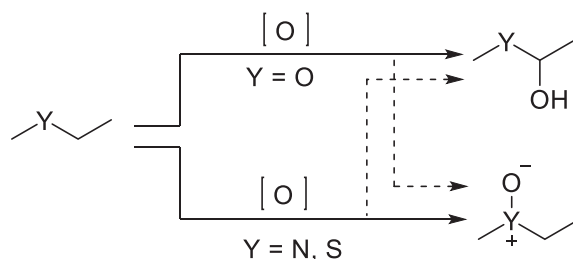
Probable peroxide formation could be described as follows; oxygen molecule **2** that has biradical structure in its ground state might withdraw proton at alpha position of oxygen atom of **1** via radical



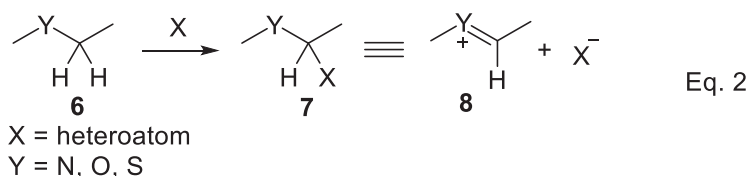
mechanism, and the carbon-centered radical **3** and hydroperoxide radical **4** might be produced. Re-combination of **3** with **4** might lead to the peroxide **5**. Electron-poor species such as carbocations and carbon-centered radicals adjacent to heteroatom could be stabilized by conjugation with lone pair on heteroatom, so oxygen biradical species could abstract proton at alpha position by radical mechanism.

The oxidation at alpha-position of heteroatom seems to be general, and similar reactions have already been reported. For example, in the Pummerer reaction,<sup>2,3</sup> sulfides are apparently oxidized at alpha-position via sulfur atom oxidation to sulfoxides and rearrangement caused by the action of acid anhydride (Scheme 1). The other example is the Polonovski reaction,<sup>4</sup> in which amines are apparently oxidized at alpha-position of nitrogen atom in a similar way as in the Pummerer reaction (Scheme 1). These reactions convert stable heteroatom-containing compounds **6** such as ethers, amines and sulfides into acetals, amins, and thioacetals **7**, which could work as reactive carbonyl group equivalents **8** (Eq. 2). So, these oxidation reactions have been utilized in synthetic organic chemistry for a long time.

As mentioned above, it is relatively easy to gain acetals and hemithioacetals from ethers and sulfides, respectively, by the oxidation at alpha-position of heteroatom, but little is known about the oxidation reactions by which amins could be produced from amines. Amins and their derivatives could be regarded as equivalents of iminium ions, reactive intermediates for Mannich reaction and Strecker



Scheme 1



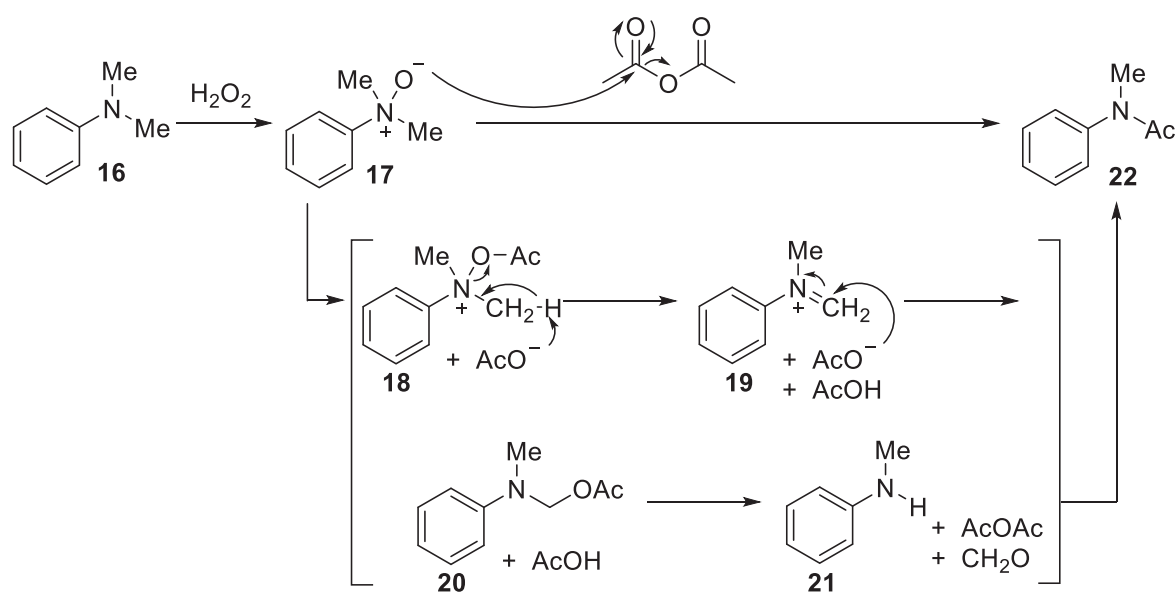
reaction, both of which are very useful reactions for synthetic organic chemistry.<sup>5</sup> If amins or their derivatives could have been synthesized more easily from amines by alpha-oxidation reaction, more efficient syntheses of nitrogen-containing compounds such as amino acids and alkaloids could be realized. So we decided to start the studies of alpha-oxidation of amines.<sup>6</sup>

Looking back the Polonovski reaction, the reaction would proceed sequentially as follows; a nitrogen atom of amines is oxygenated to give amine *N*-oxides, which are allowed to react with acid anhydride, then beta-elimination to afford iminium ions **19**. Addition of acyloxy ion to **19** gives relatively unstable amins **20**, which spontaneously degrade to give secondary amines **21** (Scheme 2). If we consider the use of amins as iminium ion equivalents, it is necessary to stabilize aminal structure to obtain amins. Our hypothesis to accomplish this is to lower the electron density of nitrogen atom of substrate molecules by acylation, or to lower the electron density of heteroatom of reagents, or both.

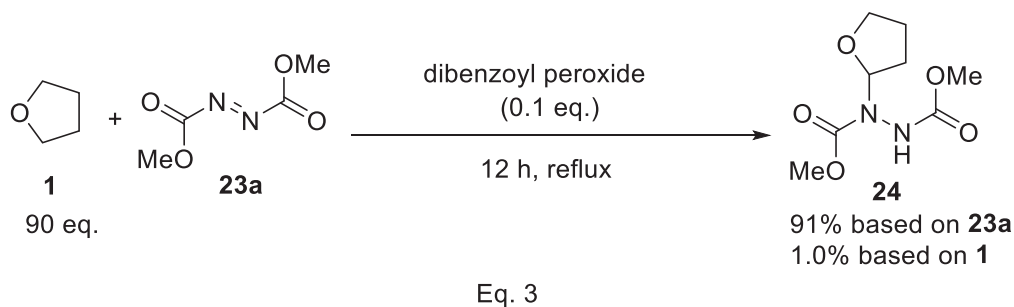
In search for reagents that meet this criteria, azodicarboxylate seemed to be a candidate molecule. Azodicarboxylate esters have been reported to react with ethers at alpha position of an oxygen atom to give amins **24** (Eq. 3).<sup>7,8</sup> This reaction has been reported to proceed in the presence of radical initiators such as acid peroxides.

This reaction seems to be a model for our research, but, some problems arose;

- (1) The reaction has been reported only for simple ether compounds such as THF and diethyl ether as substrate.<sup>7</sup>
- (2) Excess amounts of ethers are required for the efficient reaction to proceed.
- (3) There is no report of the reaction of amines as substrates (sulfides could be used as substrates).<sup>9,10</sup>



Scheme 2



## RESULTS AND DISCUSSION

*gem*-Diamino compounds, formed by reaction of amines with azodicarboxylate esters, might be unstable under acidic conditions. The use of acid peroxides as radical initiators should be avoided because these compounds would produce carboxylic acids upon reaction to proceed, that might lead to decomposition of *gem*-diamino compounds. So, reaction conditions without radical initiators must have been developed. First, we searched for azodicarboxylates that could react in the absence of radical initiators (Table 1). We used *N*-acetylpyrrolidine **25a** as a substrate because previous researches have shown that THF, that has resemble structure as **25a**, reacted with azodicarboxylate esters efficiently.<sup>9</sup> To a solution of **25a** in benzene, 1.2 eq. of ethyl azodicarboxylate **23b** was added, and the reaction mixture was stirred at reflux for 3 hr. But desired *gem*-diamino compound **26** could not be obtained, instead the substrate **25a** could be recovered in good yield (Entry 1). Dipiperidinamide **23c**,<sup>11</sup> which has been developed for Mitsunobu

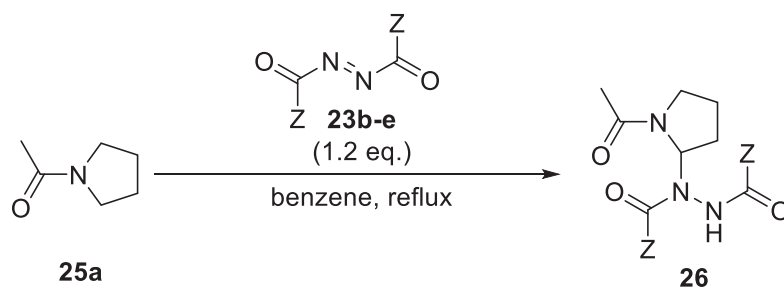


Table 1. Effect of azodicarboxylate in alpha-oxidation of amines

Entry	<b>23</b>	Z	Time (h)	<b>26</b>	Yield of <b>26</b> (%)	Recovery of <b>25a</b> (%)
1	<b>b</b>	OEt	3	<b>b</b>	0	89
2	<b>c</b>	piperidine	3	<b>c</b>	0	81
3	<b>d</b>	OPh	3	<b>d</b>	43	37
4	<b>e</b>	OCH <sub>2</sub> CCl <sub>3</sub>	3	<b>e</b>	76 *	18
5	<b>e</b>	OCH <sub>2</sub> CCl <sub>3</sub>	24	<b>f</b>	70	4

\* ; **23e** gave the highest in this series.

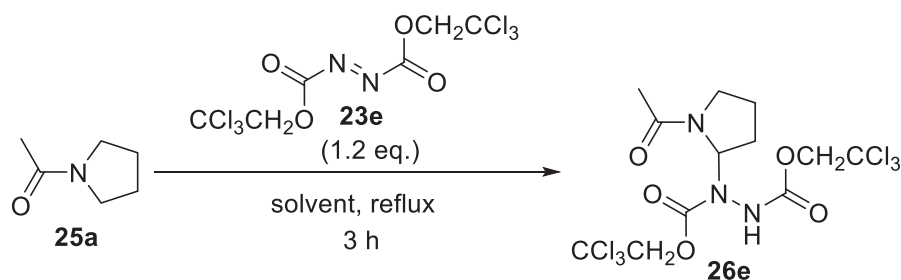


Table 2. Effect of solvent and reaction temperature in alpha-oxidation of amines

Entry	Solvent	bp of solvent (°C)	Yield of <b>26e</b> (%)	Recovery of <b>25a</b> (%)
1	benzene	80	76 (93%)	18
2	toluene	110	68	7
3	<i>p</i> -xylene	138	45	46
4	chlorobenzene	131	78 (84%)	7
5	1,2-dichloroethane	84	68	21

Yields of **26e** in parentheses are the conversion yields based on the recovery of **25a**.

reaction,<sup>12</sup> was found to be unreactive in this reaction, only to recover **25a** (Entry 2). We thought from these results that the change of ester **23b** to amide **23c** might increase the electron density on nitrogen atoms of azo group, which might lead to loss of reactivity. So, we tried other azodicarboxylates which accommodate electron-withdrawing groups on nitrogen atoms of azo group. Reaction of **23d**, which has electron-withdrawing phenoxy carbonyl group on azo group, gave desired product **26d** in moderate yield (Entry 3). The use of more electron-withdrawing trichloroethyl ester **23e** gave **26e** in much better yield than when **23d** was used (Entry 4). Longer reaction time (24 h) could not improve the yield of **26e**, presumably because the degradation of **26e** seemed to proceed (Entry 5).

Next, we examined the solvent effects (Table 2). Etheral solvents cannot be used because of their reactivity with **23e**, so, aromatic hydrocarbon solvents and haloalkane solvents were tested. The use of toluene and *p*-xylene with higher boiling points than benzene was found to lower the recovery or conversion, which might be ascribed to the decomposition of **23e** (Entries 2 & 3). The use of chlorobenzene with similar boiling point as *p*-xylene gave better yield than when toluene or *p*-xylene was used (Entry 4). This might mean that the halogen atoms in the solvent molecules could keep the stability of **23e** against heat. The use of 1,2-dichloroethane also gave good result (Entry 5). However, benzene seems to be the solvent of choice from the viewpoint of the conversion and the recovery of unreacted substrate.

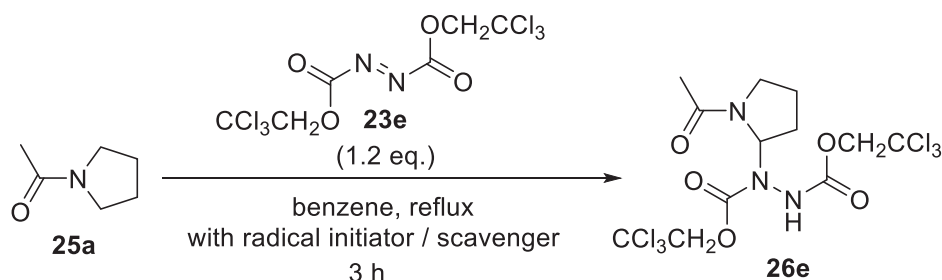
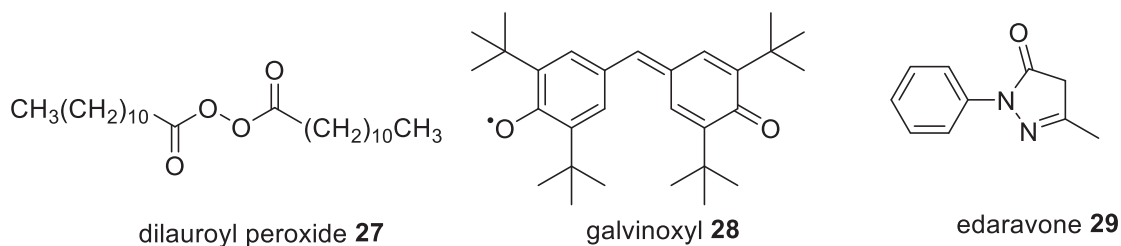
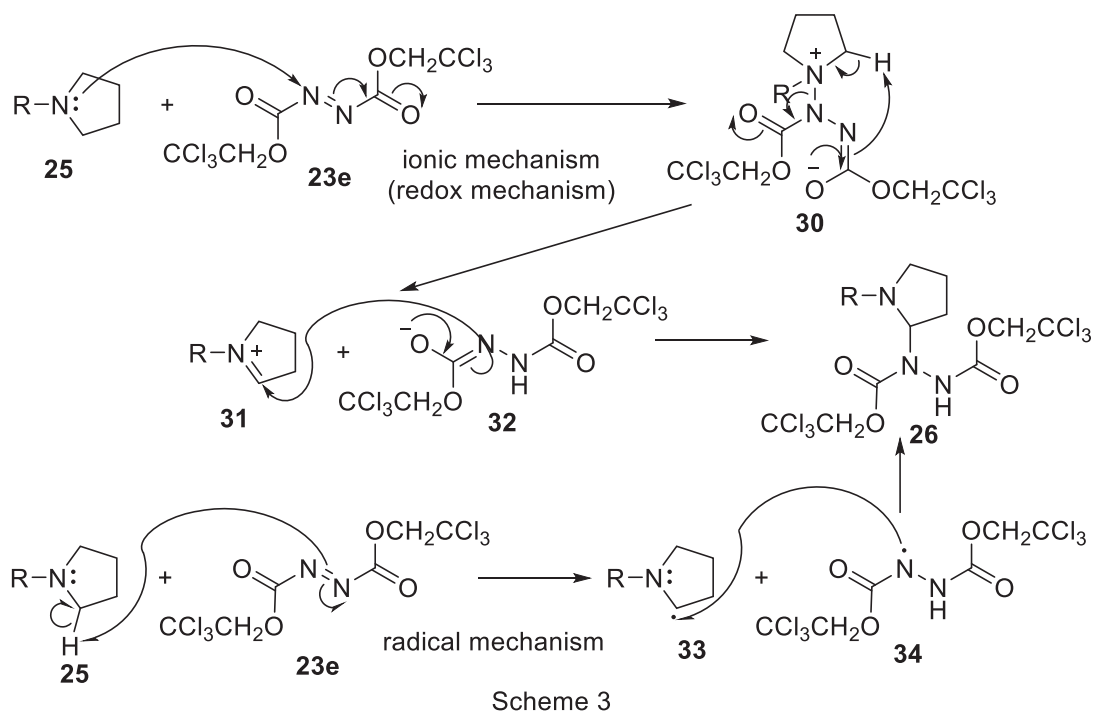


Table 3. Effect of radical initiator / scavenger in alpha-oxidation of amines

Entry	Radical initiator / scavenger	Yield of <b>26e</b> (%)	Recovery of <b>25a</b> (%)
1	dilauroyl peroxide <b>27</b> (0.1 eq.)	70	8
2	galvinoxyl <b>28</b> (0.1 eq.)	66	26
3	galvinoxyl <b>28</b> (0.3 eq.)	62	21
4	I <sub>2</sub> (0.1 eq.)	58	35
5	edaravone <b>29</b> (0.1 eq.)	53	35



It is known that azodicarboxylate esters are good electrophiles,<sup>14</sup> so the use of **23e** is reasonable when these reactions are regarded as electrophilic addition reaction of amines. On the other hand, when electron-withdrawing groups have been attached on the nitrogen atoms of azo group,  $\pi$  bond fission energies of N=N bonds might be decreased, so homolytic C-H bond fission by the attack of nitrogen centered radicals might be easier.<sup>15</sup> From this viewpoint, we examined the effects of radical initiators and radical quenchers to elucidate whether the reaction might proceed in radical or ionic mechanism (Table 3). As shown above (Entry 4 in Table 1 & Entry 1 in Table 2), reaction of **25a** with **23e** gave *gem*-diamino compound **26e** in good yield. When this reaction was performed in the presence of 0.1 eq. of radical initiator dilauroyl peroxide **27**, both of the yield of **26e** and the recovery of **25a** were somewhat decreased (Entry 1). Similarly, this reaction was performed in the presence of 0.1 eq. of radical quencher galvinoxyl **28**, I<sub>2</sub> or edaravone **29**, the yields of **26e** were remarkably decreased (Entries 2, 4 & 5). The effect of galvinoxyl **28** seemed to be only limited, because, even though the amount of added **28** was increased from 0.1 eq. to 0.3 eq., the yield of **26e** was not affected (Entry 3). From these results,



this reaction might, mainly, proceed via ionic mechanism, but radical mechanism could not be completely ruled out.

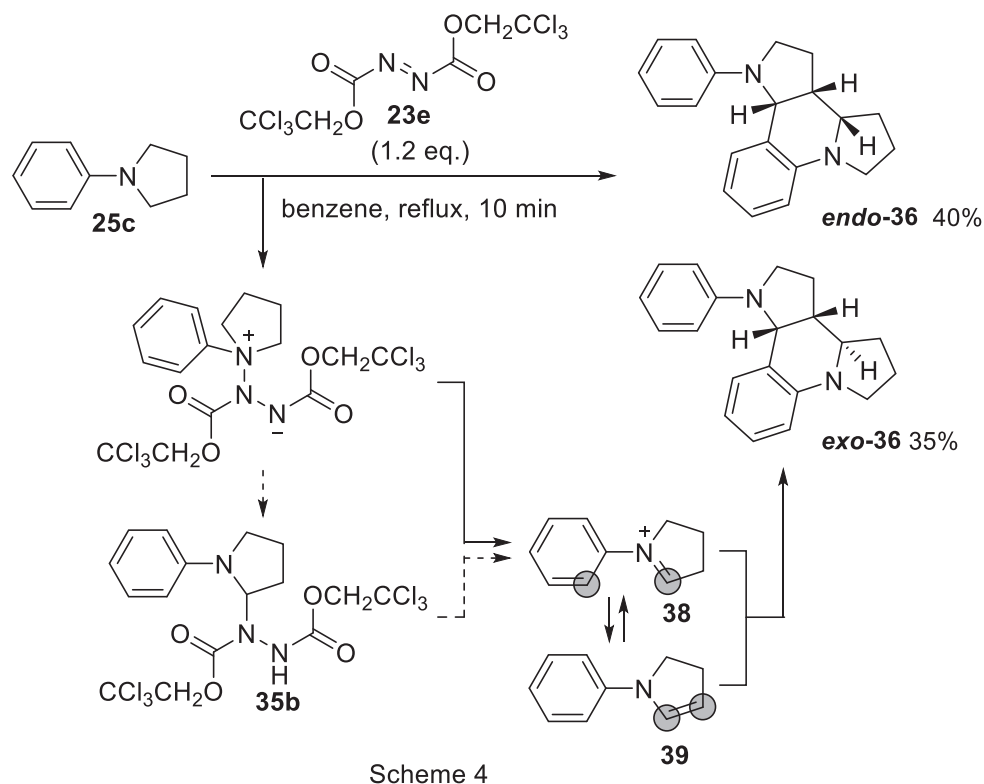
A plausible mechanism is shown in Scheme 3. Reflected by the excellent electrophilicity of **23e**, it could be assumed that the reaction would start with nucleophilic addition reaction of amine nitrogen atom to the conjugated N=N bond, and produce dipole **30**. As if breaking off the steric hindrance around the amine nitrogen atom of **30**, beta-elimination reaction of **30** would proceed to form iminium ion **31** and enolate **32**, and both molecules would rebind to give **26**. As well as the reaction of THF with azodicarboxylate ester, it also could be assumed that this reaction would proceed via radical mechanism, starting from homolysis of  $\pi$  bond in the N=N bond of **23e**, which would abstract hydrogen atom at alpha-position of the amine nitrogen atom. It could be explained that the lowering the yield of **26b** in the presence of dilauroyl peroxide **27** (Entry 1 in Table 3) might be due to the degradation of **26b** in the reaction mixture in the presence of lauric acid. The presence of galvinoxyl **28**,  $I_2$  and edaravone **29** might decompose **23e**.

### Scope and Limitations

In order to clarify the effect of the electron density on the nitrogen atom of the amine derivatives, several pyrrolidine derivatives were tested (Table 4). Pyrrolidine **25b** itself was shown only to convert **23e** to azodicarboxamide **23f** instead of desired **35a** (Entry 1). This result might be ascribed both to high elimination property of the trichloroethyl moiety, and the high nucleophilicity of unprotected pyrrolidine.



electrocyclic addition reaction of the iminium ion **38** and the enamine **39**, both of which would be produced by the thermal decomposition of **35b** (Scheme 4). It is not clear why the dimerization could occur in the case of **35b**, however, relatively high electron density of the nitrogen atom in **35b** and relatively high elimination potency of the bis(trichloroethoxycarbonyl)hydrazinyl moiety might facilitate this dimerization reaction.<sup>16</sup> These results demonstrate that secondary or tertiary amines could not be applied for this alpha-oxidation reaction because of their high nucleophilicity of nitrogen atoms.



Next, we examined the effect of protecting groups on nitrogen atom, which could control the electron density of the nitrogen atom of amines. Introduction of highly electron-withdrawing *p*-toluenesulfonyl group was found to decrease the reactivity of amine, and most of **25** was recovered unreacted (Entry 3). Attaching less electron-withdrawing benzoyl group instead of *p*-toluenesulfonyl group could recover the reactivity (Entry 4). Boc-protected derivative **25g** gave the reaction product **35f** in similar yield as **25a** (Entry 6). The use of **25i** gave 1,4-addition product **37** in good yield, presumably due to the high nucleophilicity of the active methylene group onto N=N bond (Entry 8). In order to prevent this side reaction, *gem*-dimethyl groups were introduced. But the reactivity of **25j** was found to be very low, presumably due to the steric hindrance around the nitrogen atom of **25j** (Entry 9). From these results, it was found that the steric and the electronic factors around the nitrogen atom might be very important for this reaction to proceed.

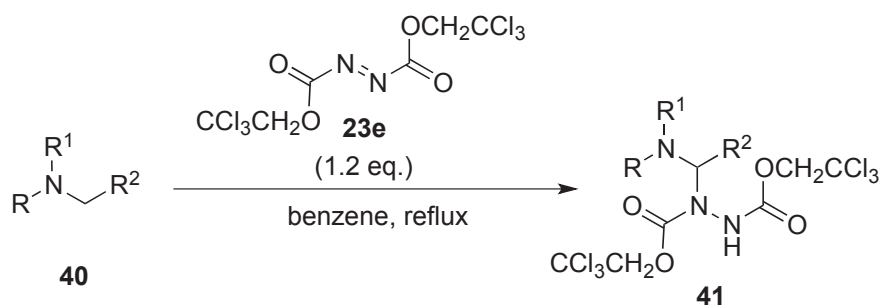


Table 5. Alpha-oxidation of various amines and azodicarboxylate

Entry	40	R	R <sup>1</sup>	R <sup>2</sup>	Time (h)	41	Yield of 41 (%)	Recovery of 40 (%)
1	<b>a</b>	Ac			12	<b>a</b>	42	51
2	<b>b</b>	Boc			12	<b>b</b>	62	24
3	<b>c</b>	Ac			3	<b>c</b>	81	7
4	<b>d</b>	Boc			3	<b>d</b>	93	-
5	<b>e</b>	Boc			12	<b>e</b>	55	37
6	<b>f</b>	Boc			12	<b>f</b>	12	85
7	<b>g</b>	Ac			12	<b>g</b>	16	82
8	<b>h</b>	Boc			12	<b>h</b>	12	85
9	<b>i</b>	Ac			12	<b>i</b>	18	68
10	<b>j</b>	Boc			12	<b>j</b>	58	41
11	<b>k</b>	Ac			12	<b>k</b>	24	45
12	<b>l</b>	Boc			12	<b>l</b>	59	22
13	<b>m</b>	H			12	<b>m</b>	32	34
14	<b>n</b>	Me			12	<b>n</b>	37	51
15	<b>o</b>	H			12	<b>o</b>	25	49
16	<b>p</b>	H			12	<b>o</b>	10	90

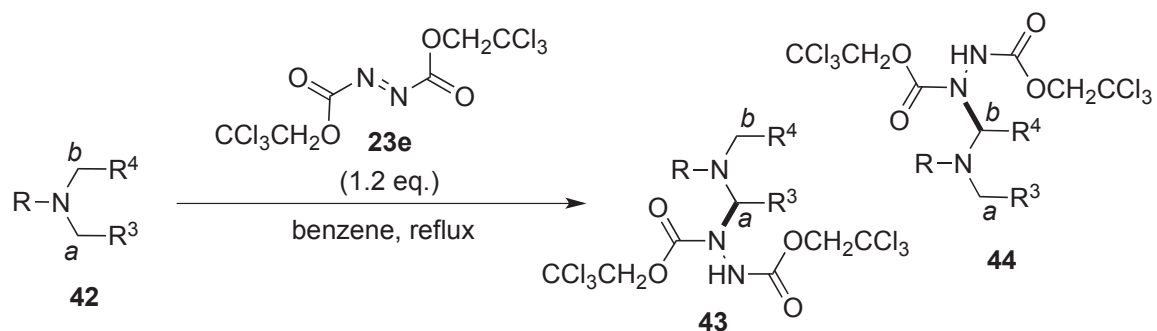


Table 6. Studies in substituent group selectivity in alpha-oxidation of amines

Entry	<b>42</b>	R	$R^3$	$R^4$	Time (h)	Yield of <b>43</b> or <b>44</b> (%)				Recovery of <b>42</b> (%)
						<b>43</b>	$a^{*1}$	<b>44</b>	$b^{*1}$	
1	<b>a</b>	Ac			3	<b>a</b>	86	<b>a</b>	-	7
2	<b>b</b>	Boc			3	<b>b</b>	96	<b>b</b>	-	-
3	<b>c</b>	Cbz			12	<b>c</b>	77	<b>c</b>	-	10
4	<b>d</b>	Boc			12	<b>d</b>	21	<b>d</b>	-	13
5	<b>e</b>	Boc			12	<b>e</b>	51	<b>e</b>	-	23
6	<b>f</b>	Boc			12	<b>f</b>	26	<b>f</b>	11	62
7	<b>g</b>	Boc			12	<b>g</b>	-	<b>g</b>	41	59
8	<b>h</b>	Boc			12	<b>h</b>	17	<b>h</b>	21	62
9	<b>i</b>	Boc			12	<b>i</b>	60	<b>i</b>	9	30
10	<b>j</b>	Boc			12	<b>j</b>	23	<b>j</b>	20	54

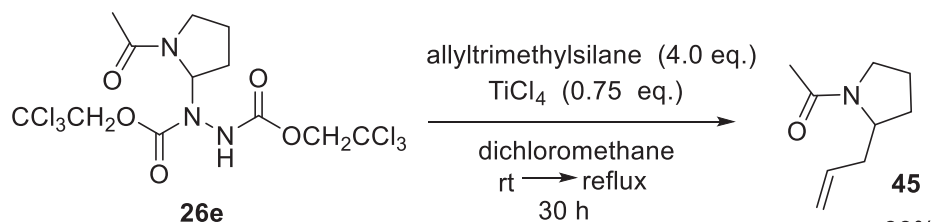
\*<sup>1</sup>);  $a$  is more highly acidic position than  $b$ .

We then examined other several secondary amine derivatives (Tables 5 & 6). We chose acetyl or Boc group as the protecting groups. First, cyclic amine derivatives were tested. 6-Membered piperidine derivatives **40a** and **40b** were found to be poor substrates for this reaction (Entries 1 & 2 in Table 5), but the reactivity of 7-membered cyclic amine derivatives **40c** and **40d** were similar to the 5-membered pyrrolidine derivatives (Entries 3 & 4 in Table 5). This tendency has also been reported in case of cyclic ether autoxidation reaction.<sup>7,8</sup> Morpholine derivatives **40g** and **40h** reacted only slightly (Entries 7 & 8), but interestingly, reaction occurred at alpha-position of the amine nitrogen atom selectively rather than the ether oxygen atom. Acyclic amine derivatives such as di-*n*-butylamine **40e** and dibenzylamine **40f** showed modest to poor conversions (Entries 5 & 6 in Table 5). From these results, it might be explained that the amine derivatives with moderately flexible structures like 5- or 7-membered ring might be more suitable for this reaction than strictly fixed structures such as 6-membered ring or highly flexible structures such as chain structures.

Next we examined the other amine derivatives, in which only one reaction site exists. Indoline derivatives **40i-j** and tetrahydroquinoline derivatives **40k-l** were found to have modest reactivity (Entries 9~12 in Table 5). Boc protected derivatives **40j** and **40l** showed better reactivity than acetyl protected derivatives **40i** and **40k**. This might come from the differences in the effects of protecting groups on the electron density on the nitrogen atom. Lactam derivatives, in which carbonyl group of amide structure is accommodated in the ring structure, were found to give the products with modest chemical yields (Entries 13~16 in Table 5). Interestingly, *N*-methylpyrrolidone **40n**, whose *N*-methyl group and 5-position of pyrrolidone ring could react, was applied for this reaction, the reaction occurred selectively at 5-position of pyrrolidone part, and the methyl group was found to be intact (Entry 14 in Table 5).

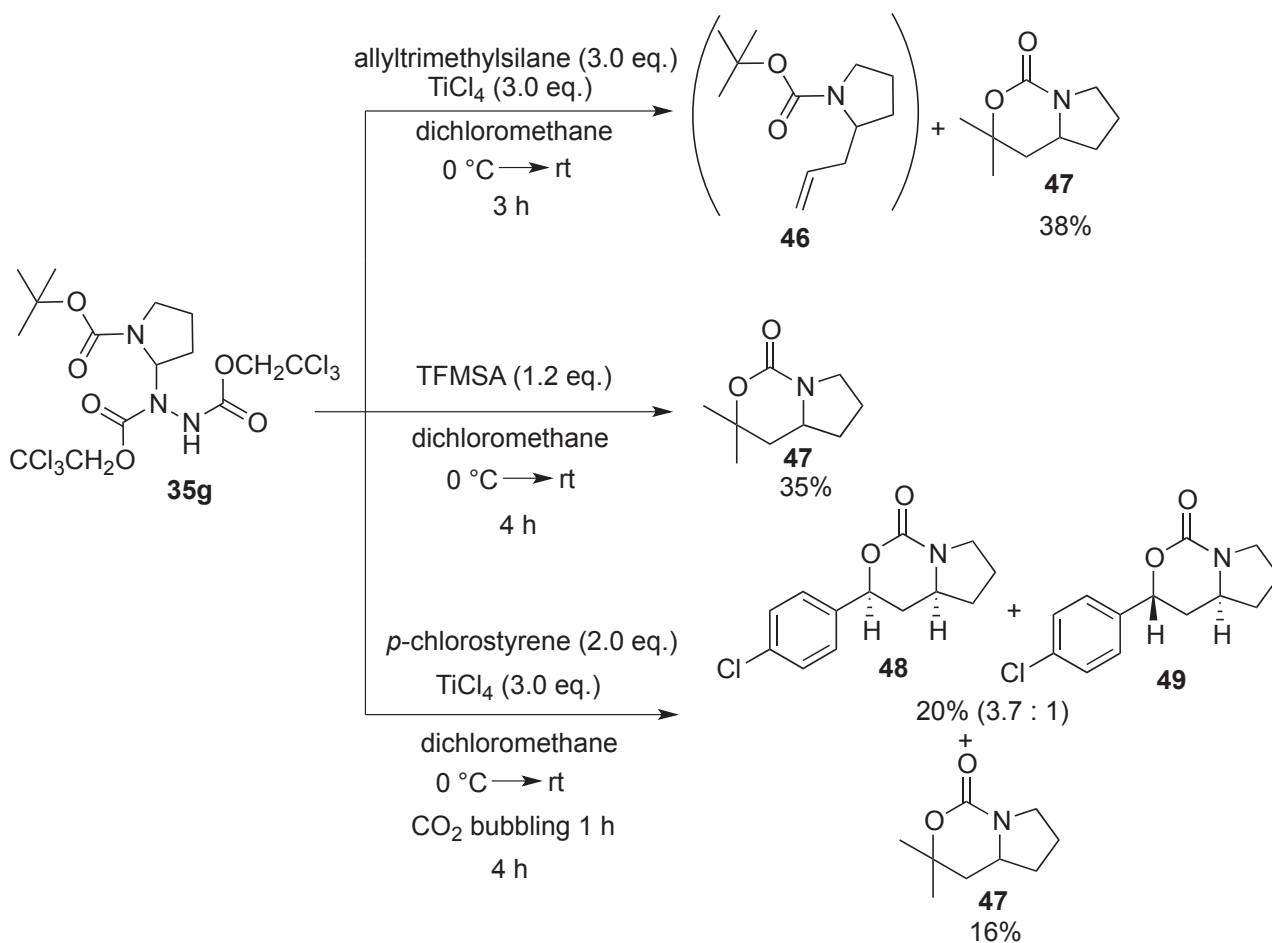
In order to clarify the effect of substituents on the nitrogen atom, asymmetric amines were examined (Table 6). Tetrahydroisoquinoline derivatives **42a**, **42b**<sup>16</sup> and tetrahydropyridine derivative **42c** were found to react selectively at methylene group put between aromatic ring and/or C=C double bond (Entries 1~3). Similarly, allylamine derivative **42d** and propargylamine derivative **42e** could react with azodicarboxylate at allylic and propargylic positions, but the yields of the products were lower as compared with **42a**, **42b** and **42c** that have cyclic structures (Entries 4 & 5). The results of reactions of benzylamine derivatives were problematic. *N*-Methylated derivative **42f** reacted at benzylic position more selectively than the methyl group (Entry 6), and *N*-ethylated derivative **42g** reacted at alpha-position in ethyl group to give **44g** (Entry 7). In case of *N*-propylated derivative **42h**, isomers **43h** whose benzylic position reacted, and **44h** whose propyl group reacted, could be obtained in almost equal amounts (Entry 8). In the case of *N*-allylated benzylamine derivative **42i**, benzylic position reacted selectively to give **43i** (Entry 9), but from *N*-propargylated benzylamine derivative **42j**, **43j** and **44j** could be obtained almost equally (Entry 10). It is not clear why this difference of reactivity would appear, but

the difference in the acidity between allylic and propargylic protons might explain this reactivity difference.<sup>17</sup> To summarize, cyclic amine derivatives (Entries 1~3) and some acyclic amine derivatives shown in Entries 4~10 appear to have tendencies to react at more acidic positions. But in case of *N*-benzylamine derivatives shown in Entries 6~10, there appear to be no rule of regioselectivity.



Eq. 4

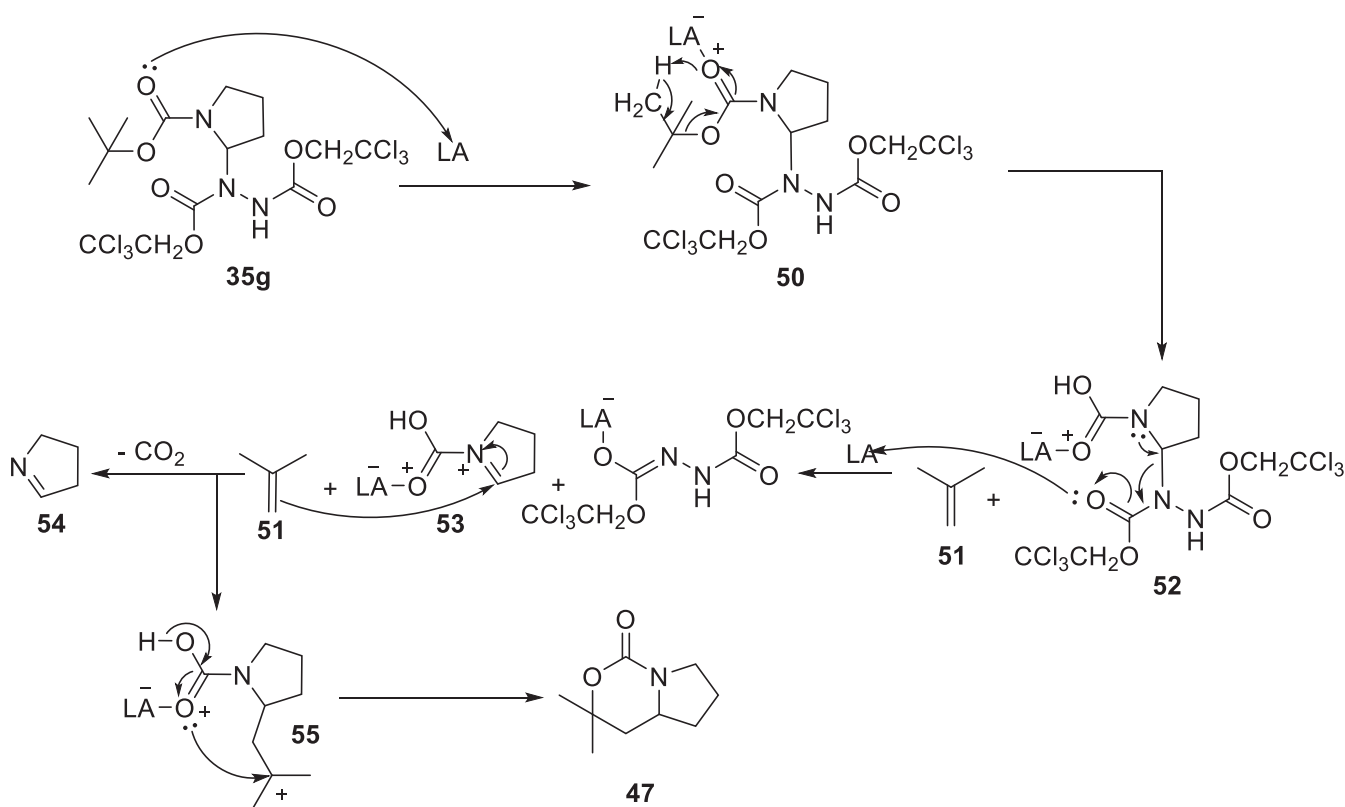
Finally, we examined the reaction of the hydrazinated products with nucleophiles in the presence of Brønsted or Lewis acid catalysts, aimed at development of carbon-carbon bond forming reactions through the formation of acyliminium ion **8** (Eq. 2). First, *gem*-diamino compound **26e** was treated with 4 eq. of



Scheme 5

allyltrimethylsilane in the presence of  $\text{TiCl}_4$ , and found to give the allylated product 2-allyl-*N*-acetylpyrrolidine **45** in good yield (Eq. 4). This result would strongly suggest that, under acidic conditions, *gem*-diamino compound **26e** could be converted to acyliminium ion as expected.

Next, we examined the reaction of Boc-protected **35g** under the same reaction condition. But, contrary to our expectation, bicyclic carbamate derivative **47** was obtained instead of  $\alpha$ -allylated derivative **46** (Scheme 5). **47** could also be obtained in the presence of TFMSA. Further, when the reaction was carried out in the presence of 2 eq. of *p*-chlorostyrene, the chlorophenyl group containing products **48** and **49** were obtained together with **47** (the relative stereochemistries of **48** and **49** were confirmed by 2D-NMR including NOESY). From these results, we can propose the reaction mechanism for **47** (Scheme 6). First, the deprotection reaction of Boc group would proceed under acidic conditions to give isobutene **51** and carbamic acid or its complex with Lewis acid **52**. Next, elimination of the hydrazinecarboxylate ester part from **52** would proceed to give acyliminium ion **53**. Imine **54** might be produced by decarboxylation of carbamic acid **52**. Instead, isobutene **51** could add to acyliminium ion **53** to give tertiary carbocation **55**, and further intramolecular attack of carbamic acid group could give the bicyclic carbamate **47**. We expect that further development of this reaction would pave the way for the efficient syntheses of nitrogen-containing heterocycles because the conversion of **25g** to **47** is shown to be atom-economical, no change of the number of carbon atom.



Scheme 6

In conclusion, we could develop an oxidation reaction at alpha-position of protected amines using bis(trichloroethyl) azodicarboxylate **23e**. The reaction enables to convert relatively stable amines to reactive iminium ion equivalents, which are very useful reaction intermediates in synthetic organic chemistry. Scope and limitations of this reaction could not fully elucidated, but a tendency of reactivity of cyclic amines could be estimated from their structural features. The reaction products, *gem*-diamino compounds, could be verified to function as the precursors of acyliminium ions. Moreover, we are confident that the discovery of the reaction of **35g** in the presence of Lewis- or Brønsted acids to give 1,3-oxazinan-2-one derivatives, in which *tert*-butyl group of Boc group could be incorporated in the product molecules, will lead to development of highly atom-economical carbon-carbon bond forming reactions. We expect that our study will become one of the methodology that make efficient organic synthesis possible.

## EXPERIMENTAL

IR spectra were recorded on JASCO FT/IR-460 plus. NMR spectra were measured on JEOL JNM-A-400, using tetramethylsilane (0.00 ppm) for <sup>1</sup>H NMR spectra, and chloroform-*d* (77.10 ppm) for <sup>13</sup>C NMR as internal standards. Chemical shifts ( $\delta$ ) were reported by ppm, and coupling constants (*J*) were reported by Hz. Signal multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), broad signal (br), respectively. NMR yields were estimated by using bromoform (singlet at 6.83 ppm) as an internal standard. EIMS and FABMS spectra were recorded on JEOL JMS-700. Dry tetrahydrofuran (THF) and dichloromethane (Kanto Co. Ltd.) were used as received, and benzene was distilled from sodium. Column chromatography was carried out by using Silica Gel 60 N (Kanto Co. Ltd., spherical, neutral) 63-210  $\mu$ m as stationary phase. Azodicarboxylates **23d**<sup>18</sup> and **23e**,<sup>19,20</sup> and starting materials **25a**,<sup>14</sup> **25c**,<sup>21,22</sup> **25d**,<sup>23</sup> **25e**,<sup>24</sup> **25f**,<sup>25,26</sup> **25g**,<sup>27,28</sup> **40a**,<sup>15</sup> **40b**,<sup>28</sup> **40c**,<sup>29</sup> **40d**,<sup>30</sup> **40e**,<sup>31</sup> **40f**,<sup>32</sup> **40g**,<sup>33</sup> **40h**,<sup>28</sup> **40i**,<sup>34</sup> **40j**,<sup>34</sup> **40k**,<sup>35,36</sup> **40l**,<sup>34</sup> **42a**,<sup>37</sup> **42b**,<sup>31</sup> **42c**,<sup>38</sup> **42e**,<sup>39</sup> **42f**,<sup>40</sup> **42g**<sup>41</sup> were prepared according to the literature procedures.

### 2,2,2-Trichloroethyl pyrrolidine-1-carboxylate (**25h**)

Pyrrolidine **25b** (1.66 mL, 19.9 mmol) and triethylamine (8.4 mL, 60.3 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (70 mL), and cooled on ice. 2,2,2-Trichloroethyl chloroformate (3.3 mL, 24.0 mmol) was added, and stirred at room temperature for 4 h. The reaction was quenched by adding water, and organic layer was washed twice with 5% aqueous HCl solution, once with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated.

<sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.85~1.93 (m, 4H), 3.41~3.52 (m, 4H), 4.74 (s, 4H). <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  24.91, 25.60, 45.93, 46.42, 74.79, 95.87, 152.96. IR (KBr) 2981, 1729, 722 cm<sup>-1</sup>. EIMS *m/z* 246

(M<sup>+</sup>), 245 (M<sup>+1</sup>), 210, 114 (100%), 98. HR-MS calcd. for C<sub>7</sub>H<sub>10</sub><sup>35</sup>Cl<sub>3</sub>NO<sub>2</sub> (M<sup>+</sup>) 244.9777, found. 244.9779.

### 1-(Pyrrolidin-1-yl)butane-1,3-dione (25i)

Pyrrolidine **25b** (1.7 mL, 20.4 mmol) was dissolved in THF (80 mL), and cooled on ice. Diketene (2.3 mL, 30.0 mmol) was added, and stirred at room temperature for 8 h. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (*n*-hexane : EtOAc = 1 : 1 *v/v*) and distillation (300 Pa, 118 °C) to give **25i** (1.77 g, 57%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.80~2.05 (m, 5H), 2.30 (s, 2H), 3.30~3.55 (m, 5.5H), 4.97 (s, 0.28H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 21.59, 24.27, 25.60, 25.86, 30.25, 44.74, 45.72, 45.93, 47.04, 51.13, 164.81, 170.13, 173.95, 202.41. IR (neat) 2973, 1718, 1684 cm<sup>-1</sup>.

### 2,2-Dimethyl-1-(pyrrolidin-1-yl)pentane-1,3-dione (25j)

**25i** (2.30 g, 14.8 mmol) was dissolved in DMF (50 mL), and cooled on ice. NaH (60% in oil, 0.712 g, 17.8 mmol) and iodomethane (0.92 mL, 14.8 mmol) were added, and stirred at room temperature for 3.5 h. The mixture was cooled on ice, and iodomethane (0.92 mL, 14.8 mmol) and NaH (60% in oil, 0.295 g, 7.38 mmol) were added, and stirred at room temperature for 4 h. Again, the mixture was cooled on ice, and iodomethane (1.84 mL, 29.6 mmol) and NaH (60% in oil, 0.710 g, 17.8 mmol) were added, and stirred at room temperature for 4 h. The reaction was quenched by adding water, and extracted with CH<sub>2</sub>Cl<sub>2</sub>. Organic layer was washed with water and saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*), and distillation (200 Pa, 112 °C) gave **25j** (0.308 g, 11%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.07 (t, *J* = 7.2 Hz, 3H), 1.36 (s, 6H), 1.77~1.90 (m, 4H), 2.45 (q, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 3.52 (t, *J* = 6.8 Hz, 2H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 8.17, 22.30, 23.18, 26.54, 30.90, 46.33, 47.22, 56.05, 170.87, 211.20. IR (neat) 2977, 1712, 1633 cm<sup>-1</sup>. EIMS *m/z*: 197 (H<sup>+</sup>), 141 (100%), 112, 98. HR-MS calcd. for C<sub>11</sub>H<sub>19</sub>NO<sub>2</sub> (H<sup>+</sup>) 197.1416, found. 197.1416.

### *t*-Butyl allyl(ethyl)carbamate (42d)

Ethylamine hydrochloride (2.81 g, 34.5 mmol) and triethylamine (14.4 mL, 103 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and cooled on ice. A solution of di-*t*-butyl dicarbonate (7.69 g, 35.2 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (15 mL) was added, and stirred at room temperature for 14.5 h. The mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed twice with 5% aqueous HCl solution, once with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated to give crude *t*-butyl ethylcarbamate (4.36 g, 87%).

Crude *t*-butyl ethylcarbamate (3.77 g, 26.0 mmol) and allyl bromide (4.5 mL, 52.0 mmol) were dissolved in DMF (87 mL), and cooled on ice. NaH (60% in oil, 2.23 g, 55.8 mmol) was added, and stirred at room temperature for 4.5 h. After cooled on ice, the reaction was quenched by adding water. The mixture was diluted with Et<sub>2</sub>O, washed with 5% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 30 : 1 *v/v*), and distillation (3.0 kPa, 89 °C) gave **42d** (1.73 g, 36%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.08 (t, *J* = 7.2 Hz, 3H), 1.46 (s, 9H), 3.05 (br, 2H), 3.70~3.90 (br, 2H).

<sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 13.45, 28.43, 49.06, 79.22, 115.92, 155.37. IR (neat) 2976, 1698 cm<sup>-1</sup>.

#### ***t*-Butyl benzyl(propyl)carbamate (42)**

Propylamine (2.6 mL, 31.6 mmol) and triethylamine (8.6 mL, 61.7 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), and cooled on ice. A solution of di-*t*-butyl dicarbonate (6.88 g, 31.5 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added, and stirred at room temperature for 17.5 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, washed twice with 5% aqueous HCl solution, once with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated to give crude *t*-butyl propylcarbamate (5.02 g, 100%).

Crude *t*-butyl propylcarbamate (2.82 g, 17.7 mmol) and benzyl bromide (2.75 mL, 23.1 mmol) were dissolved in DMF (52 mL), and cooled on ice. NaH (60% in oil, 1.03 g, 25.7 mmol) was added, and stirred at room temperature for 4 h. After cooled on ice, the reaction was quenched by adding water, and the mixture was diluted with Et<sub>2</sub>O, washed with 5% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 50 : 1 *v/v*), and distillation (200 Pa, 117 °C) gave **42h** (2.84 g, 64%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.85 (t, *J* = 7.2 Hz, 3H), 1.35~1.60 (m, 11H), 2.98~3.28 (m, 4H), 4.34~4.52 (br, 2H), 7.17~7.36 (m, 4H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 11.22, 21.09, 21.32, 48.28, 49.78, 50.39, 79.39, 126.96, 126.96, 127.58, 128.35, 138.55, 155.63. IR (neat) 2968, 1694 cm<sup>-1</sup>. EIMS *m/z*: 249 (M<sup>+</sup>), 193, 164, 120, 86, 84 (100%).

#### ***t*-Butyl allyl(benzyl)carbamate (42i)**

Allylamine (4.8 mL, 64.0 mmol) and triethylamine (13.5 mL, 96.9 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (180 mL), and cooled on ice. A solution of di-*t*-butyl dicarbonate (14.0 g, 64.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added, and stirred at room temperature for 16 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed twice with 5% aqueous HCl solution, once with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated to give crude *t*-butyl allylcarbamate (10.1 g, 100%).

Crude *t*-butyl allylcarbamate (5.76 g, 36.6 mmol) and benzyl bromide (6.6 mL, 55.5 mmol) were dissolved in DMF (110 mL), and cooled on ice. NaH (60% in oil, 2.36 g, 59.1 mmol) was added, and stirred at room temperature for 2 h. After cooled on ice, the reaction was quenched by adding water. The mixture was diluted with Et<sub>2</sub>O, washed with 5% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : Et<sub>2</sub>O = 15 : 1 *v/v*), and distillation (500 Pa, 125 °C) gave **42i** (5.93g, 66%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.42~1.52 (br, 9H), 3.65~3.95 (m, 2H), 4.30~4.50 (br, 2H), 5.00~5.25 (m, 2H), 5.65~5.87 (br, 2H), 7.19~7.39 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.39, 48.61, 48.80~49.70 (br), 79.79, 116.00~117.20 (br), 127.09, 127.30, 127.76, 128.43, 133.69, 138.30, 155.80. FABMS (Yokudel<sup>®</sup>) *m/z*: 248.1 ([M+H]<sup>+</sup>), 192.1 (100%). HR-MS calcd. for C<sub>15</sub>H<sub>22</sub>NO<sub>2</sub> ([M+H]<sup>+</sup>) 248.1650, found. 248.1660.

#### ***t*-Butyl benzyl(propargyl)carbamate (42j)**

Benzylamine (2.6 mL, 23.8 mmol) and triethylamine (6.6 mL, 47.4 mmol) were dissolved in CH<sub>2</sub>Cl<sub>2</sub> (80 mL), and cooled on ice. A solution of di-*t*-butyl dicarbonate (5.25 g, 24.1 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added, and stirred at room temperature for 18.5 h. The reaction mixture was diluted with CH<sub>2</sub>Cl<sub>2</sub>, and washed twice with 5% aqueous HCl solution, once with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated to give crude *t*-butyl benzylcarbamate (4.83 g, 98%).

Crude *t*-butyl benzylcarbamate (3.14 g, 15.1 mmol) and propargyl bromide (9.2 M solution in toluene, 2.3 mL, 21.4 mmol) were dissolved in DMF (48 mL), and cooled on ice. NaH (60% in oil, 0.932 g, 23.3 mmol) was added, and stirred at room temperature for 4 h. After cooled on ice, the reaction was quenched by adding water. The mixture was diluted with Et<sub>2</sub>O, washed with 5% aqueous Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 50 : 1 *v/v*), and distillation (500 Pa, 134 °C) gave **42j** (2.84g, 64%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.44~1.54 (m, 9H), 2.18~2.24 (m, 1H), 3.83~4.12 (m, 2H), 4.55 (s, 2H), 7.23~7.38 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.29, 35.16, 49.20, 71.00~72.50 (br), 79.24, 80.48, 127.31, 127.58, 128.01, 128.45, 137.39, 155.00. IR (neat) 3293, 2977, 1698 cm<sup>-1</sup>.

#### **Diphenyl 1-(1-acetylpyrrolidin-2-yl)hydrazine-1,2-dicarboxylate (26a)**

**25a** (0.113 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23d** (0.324 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **26a** (0.166 g,

43%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.80~2.02 (br, 1H), 2.05~2.55 (m, 6H), 3.44~3.58 (m, 1H), 3.60~3.82 (br, 1H), 5.05~5.40 (br, 1H), 6.00~6.35 (m, 1H), 7.08~7.44 (m, 10H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.95, 22.18, 22.70, 23.39, 28.80~30.70 (br), 31.07, 71.17, 121.13, 121.19, 121.60, 125.54, 125.63, 125.87, 129.21, 129.28, 129.40, 150.52, 150.76, 153.58, 155.18, 170.88, 171.08, 171.56. IR (KBr) 3190, 2975, 1732, 1635, 1194  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 384.0 ( $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 340.1, 112.0 (100%). HR-MS calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_3\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 384.1559, found. 384.1554.

### **Bis(2,2,2-trichloroethyl) 1-(1-acetylpyrrolidin-2-yl)hydrazine-1,2-dicarboxylate (26b)**

**25a** (0.113 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 2 : 1 v/v) gave **26b** (0.374 g, 76%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.80~2.00 (br, 1H), 2.05~2.16 (m, 3H), 2.08~2.65 (m, 3H), 3.40~3.94 (m, 2H), 4.38~5.23 (m, 4H), 5.82~6.22 (m, 1H), 6.50~6.70 (br, 1H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.94, 22.14, 22.23, 22.85, 28.50~30.50, 46.81, 48.23, 70.45~73.00, 74.89, 75.33, 75.76, 94.76, 95.00, 153.10, 155.12, 170.81, 171.46. IR (KBr) 3181, 2955, 1762, 1727, 1638, 1214, 720  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 493.8 ( $\text{C}_{12}\text{H}_{16}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 491.8 ( $\text{C}_{12}\text{H}_{16}^{35}\text{Cl}_6\text{N}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 184.1, 128.0 (100%), 112.0, 84.1. HR-MS calcd. for  $\text{C}_{12}\text{H}_{16}^{35}\text{Cl}_6\text{N}_3\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 491.9221, found. 491.9209.

### **1,1'-(Azodicarbonyl)dipyrrolidine (23f)**

Pyrrolidine **25b** (0.17 mL, 2.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.380 g, 1.0 mmol) was added, and stirred at reflux for 4 min. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (EtOAc) gave **23f** (0.170 g, 76%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.95~2.03 (m, 8H), 3.54 (t,  $J = 5.6$  Hz, 4H), 3.67 (t,  $J = 5.6$  Hz, 4H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  24.14, 26.02, 46.55, 46.83, 159.88. IR (KBr) 2924, 1718, 1695  $\text{cm}^{-1}$ .

### **(3aR\*,3bS\*,11bR\*)-1-Phenyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinoline (cis-36a)**

**25c** (0.147 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 10 min. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 100 : 1 v/v) gave *cis*-dimer **cis-36a** (0.0584 g, 40%) and *trans*-dimer **trans-36b** (0.0510 g, 35%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.65~1.76 (m, 1H), 1.78~2.16 (m, 5H), 2.46~2.56 (m, 1H), 3.22~3.50 (m, 4H), 3.70~3.76 (m, 1H), 5.11 (d,  $J = 6.8$  Hz, 1H), 6.39 (dd,  $J = 1.2, 7.6$  Hz, 1H), 6.69 (tt,  $J = 1.2, 7.6$  Hz, 1H), 6.81 (d,  $J = 8.0$  Hz, 2H), 7.05~7.15 (m, 1H), 7.23~7.35 (m, 3H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.15, 23.25, 30.16, 39.99, 46.53, 47.34, 56.35, 57.36, 110.18, 111.17, 115.33, 115.72, 122.88, 127.97, 128.73, 129.27, 143.09, 148.76. IR (KBr) 3287, 2957, 1733, 1423, 1134, 718  $\text{cm}^{-1}$ . EIMS  $m/z$  290 ( $\text{M}^+$ ), 184, 170 (100%). HR-MS calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_2$  ( $\text{M}^+$ ) 290.1783, found. 290.1778.

**(3aR\*,3bR\*,11bR\*)-1-Phenyl-2,3,3a,3b,4,5,6,11b-octahydro-1H-dipyrrolo[1,2-a:3',2'-c]quinoline (trans-36b)**

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68~1.85 (m, 2H), 1.90~2.05 (m, 1H), 2.08~2.32 (m, 3H), 2.46 (td,  $J = 7.2, 10.0$  Hz, 1H), 2.72~2.85 (m, 1H), 2.85 (q,  $J = 8.9$  Hz, 1H), 3.27~3.47 (m, 1H), 3.46 (dt,  $J = 3.4, 8.9$  Hz, 1H), 3.63~3.69 (m, 1H), 4.45 (d,  $J = 8.9$  Hz, 1H), 6.65~6.76 (m, 4H), 6.78 (dt,  $J = 1.2, 7.6$  Hz, 1H), 7.11 (td,  $J = 1.2, 7.6$  Hz, 1H), 7.15~7.27 (m, 3H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.28, 30.52, 31.95, 47.22, 48.19, 49.10, 59.42, 64.57, 112.06, 112.66, 116.42, 118.83, 126.95, 127.14, 128.23, 129.02, 147.11, 149.15. IR (KBr) 2899, 2861, 2838, 751, 693  $\text{cm}^{-1}$ . EIMS  $m/z$  290 ( $\text{M}^+$ ), 184, 170 (100%). HR-MS calcd. for  $\text{C}_{20}\text{H}_{22}\text{N}_2$  ( $\text{M}^+$ ) 290.1783, found. 290.1790.

**Bis(2,2,2-trichloroethyl) 1-{1-(*p*-toluensulfonyl)pyrrolidin-2-yl}hydrazine-1,2-dicarboxylate (35c)**

**25d** (0.233 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 7.5 : 1 v/v) gave **35c** (0.116 g, 23%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.50~1.65 (m, 2H), 1.80~2.05 (m, 2H), 2.07~2.30 (m, 1H), 2.45 (s, 3H), 3.05~3.20 (m, 1H), 3.60~3.80 (m, 1H), 4.40~5.25 (m, 4H), 5.65~5.85 (m, 1H), 7.08 (s, 1H), 7.37 (d,  $J = 7.6$  Hz, 2H), 7.80 (d,  $J = 7.6$  Hz, 2H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.53, 22.64, 23.16, 30.46, 30.58, 31.37, 48.98, 49.08, 71.40, 71.68, 74.85, 74.99, 75.27, 75.58, 76.00, 94.49, 94.63, 94.75, 127.31, 127.65, 129.90, 133.01, 133.16, 144.22, 153.46, 153.91, 154.43. IR (KBr) 3293, 2958, 1737, 1163, 666  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 605.7 ( $\text{C}_{17}\text{H}_{20}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6\text{S}$ : [ $\text{M}+\text{H}$ ] $^+$ ), 603.7 ( $\text{C}_{17}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6\text{S}$ : [ $\text{M}+\text{H}$ ] $^+$ ), 224.0 (100%). HR-MS calcd. for  $\text{C}_{17}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6\text{S}$  ([ $\text{M}+\text{H}$ ] $^+$ ) 603.9204, found. 603.9224.

**Bis(2,2,2-trichloroethyl) 1-(1-benzoylpyrrolidin-2-yl)hydrazine-1,2-dicarboxylate (35d)**

**25f** (0.175 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 5 : 1 v/v) gave **35d** (0.221 g,

40%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.68~1.90 (br, 1H), 1.96~2.17 (br, 1H), 2.25~2.80 (m, 2H), 3.40~3.60 (br, 1H), 3.60~4.00 (m, 1H), 4.40~5.25 (m, 4H), 5.30~5.50 (br, 1H), 5.90~6.40 (br, 1H), 7.37~7.60 (m, 5H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.00~26.00 (br), 27.00~32.00 (br), 70.50~73.00 (br), 74.92, 78.40~80.00 (br), 94.89, 127.27, 128.28, 130.55, 135.74, 151.00~156.00 (br), 170.54. IR (KBr) 3198, 2956, 1735, 1628, 1397, 1216, 1108, 720  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 555.8 ( $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 553.8 ( $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_6\text{N}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 174.0 (100%), 104.9, 77.1. HR-MS calcd. for  $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_6\text{N}_3\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 553.9338, found. 553.9357.

**Bis(2,2,2-trichloroethyl) 1-{1-(4-methoxybenzoyl)pyrrolidin-2-yl}hydrazine-1,2-dicarboxylate (35e)**

**25f** (0.205 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 2 : 1 *v/v*) gave **35e** (0.234 g, 40%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.70~1.87 (br, 1H), 1.95~2.17 (br, 1H), 2.15~2.55 (br, 1H), 2.55~2.80 (br, 1H), 3.47~3.60 (br, 1H), 3.60~4.00 (br, 1H), 4.50~5.10 (m, 4H), 5.25~5.55 (br, 1H), 6.00~6.35 (br, 1H), 6.91 (dd,  $J = 3.2, 8.4$  Hz, 2H), 7.48~7.58 (m, 2H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  23.88, 24.90, 28.29, 50.05, 55.13, 70.50~72.50 (br), 74.72, 74.72~76.00 (br), 77.50~79.50 (br), 94.70, 94.87, 113.27, 127.68, 129.30, 151.00~155.80 (br), 161.04, 169.10~170.80. IR (KBr) 3207, 2957, 1735, 1609, 1395, 1255, 719  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 585.8 ( $\text{C}_{18}\text{H}_{20}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 583.7 ( $\text{C}_{20}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 204.0, 135.0 (100%). HR-MS calcd. for  $\text{C}_{18}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 583.9483, found. 583.9459.

**Bis(2,2,2-trichloroethyl) 1-{1-(*t*-butoxycarbonyl)pyrrolidin-2-yl}hydrazine-1,2-dicarboxylate (35f)**

**25g** (0.171 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **35f** (0.125 g, 20%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.46 (s, 9H), 1.75~1.90 (br, 1H), 1.85~2.10 (br, 1H), 2.10~2.40 (br, 2H), 3.24~3.64 (m, 2H), 4.40~5.25 (m, 4H), 5.74~6.10 (br, 1H), 6.55~6.90 (br, 1H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.65, 28.34, 30.20~31.90 (br), 45.50~47.30 (br), 70.00~72.50 (br), 74.50~76.00 (br), 80.00~82.50 (br), 94.55, 94.73, 152.00~155.00. IR (KBr) 3275, 2979, 1733, 1701, 1682, 1166, 724  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 598.8 ( $\text{C}_{19}\text{H}_{22}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 596.8 ( $\text{C}_{19}\text{H}_{22}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 543.8, 449.8, 170.0, 113.9 (100%), 70.3. HR-MS calcd. for  $\text{C}_{19}\text{H}_{22}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 549.9640, found. 549.9656.

**Bis(2,2,2-trichloroethyl) 1-[1-{(2,2,2-trichloroethoxy)carbonyl}pyrrolidin-2-yl]hydrazine-1,2-dicarboxylate (39d)**

**25d** (0.247 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **26c** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 20 : 1 *v/v*) gave **39d** (0.125 g, 20%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.58~1.70 (m, 1H), 1.84~1.98 (m, 1H), 1.98~2.18 (br, 1H), 2.20~2.45 (br, 1H), 3.46~3.76 (m, 2H), 4.40~5.20 (m, 4H), 5.85~6.30 (br, 1H), 6.70~6.95 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 22.48, 23.00, 28.50~31.00 (br), 30.70~32.00 (br), 46.85, 47.45, 70.10~72.00 (br), 74.84, 74.99, 75.22, 75.53, 76.22, 76.29, 93.70, 94.39, 94.40~94.80 (br), 95.03, 95.22, 149.78, 149.80, 152.30~153.10 (br), 153.14, 153.30~155.30 (br). IR (KBr) 3287, 2957, 1733, 1423, 1134, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 627.6 (C<sub>13</sub>H<sub>15</sub><sup>35</sup>Cl<sub>7</sub><sup>37</sup>Cl<sub>2</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 623.7 (C<sub>13</sub>H<sub>15</sub><sup>35</sup>Cl<sub>9</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 243.9 (100%). HR-MS calcd. for C<sub>13</sub>H<sub>15</sub><sup>35</sup>Cl<sub>9</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 623.8157, found. 623.8182.

**Bis(2,2,2-trichloroethyl) 1-{1,3-dioxo-1-(pyrrolidin-1-yl)but-2-yl}hydrazine-1,2-dicarboxylate (37)**

**25i** (0.155 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 6 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*) gave **37** (0.463 g, 86%) as colorless liquid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.80~2.15 (m, 4H), 2.25~2.55 (m, 3H), 3.20~4.00 (m, 4H), 4.50~5.00 (m, 4H), 5.52~5.80 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 24.06, 25.84, 27.72, 27.90, 46.32, 46.34, 46.59, 68.86, 70.32, 74.74, 74.82, 75.99, 94.27, 94.33, 94.61, 94.71, 153.60, 153.99, 154.11, 154.87, 160.50~163.80, 198.70~202.10. IR (neat) 3284, 2958, 1771, 1738, 1705, 1650, 1215, 722 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 535.9 (C<sub>14</sub>H<sub>18</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>) (100%), 533.9 (C<sub>14</sub>H<sub>18</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 159.0, 144.0. HR-MS calcd. for C<sub>14</sub>H<sub>18</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 533.9327 found 533.9330.

**Bis(2,2,2-trichloroethyl) 1-{1-(2,2-dimethyl-3-oxopentanoyl)pyrrolidin-2-yl}hydrazine-1,2-dicarboxylate (35i)**

**25j** (0.278 g, 1.41 mmol) was dissolved in benzene (4.7 mL), **23e** (0.643 g, 1.69 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*) gave **35i** (0.117 g, 23%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.95~1.20 (m, 6H), 1.27~1.55 (m, 6H), 1.60~1.95 (m, 1H), 1.90~2.60 (m, 3H), 2.85~3.17 (m, 1H), 3.20~3.40 (m, 1.5H), 3.50~3.70 (br, 0.5H), 4.35~5.30 (m, 4H), 5.90~6.22 (br,

0.5H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.25, 20.39, 21.58, 23.02, 23.37, 24.15, 24.71, 27.41, 27.59, 28.00~30.00 (br), 35.48, 35.72, 36.10, 71.50~73.00 (br), 74.82, 75.77, 80.02, 80.59, 94.79, 151.50~155.00 (br), 171.95, 214.02. IR (KBr) 3310, 2987, 1765, 1743, 1682, 1644, 1222, 712  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$  577.8 ( $\text{C}_{17}\text{H}_{24}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 575.9 ( $\text{C}_{17}\text{H}_{23}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 196.1 (100%). HR-MS calcd. for  $\text{C}_{17}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 575.9796, found. 575.9796.

#### **Bis(2,2,2-trichloroethyl) 1-(1-acetylpyrrolidin-2-yl)hydrazine-1,2-dicarboxylate (41a)**

**40a** (0.127 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*) gave **41a** (0.211 g, 42%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.40~1.60 (br, 1H), 1.53~1.75 (br, 2H), 1.80~1.98 (br, 2H), 2.13 (s, 3H), 2.80~3.10 (m, 0.5H), 3.30~3.87 (m, 1.5H), 4.40~5.15 (m, 4H), 5.60~6.15 (m, 0.5H), 6.93~6.15 (br, 1H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.13, 19.00~20.20.50 (br), 21.51, 21.70~23.60 (br), 22.95, 23.40~25.30 (br), 27.00~29.90 (br), 38.10, 38.38, 41.30~42.20 (br), 44.20~46.60 (br), 66.00~68.00 (br), 74.84, 75.20, 75.46, 94.73, 94.92, 152.85, 153.42, 171.20, 172.39. IR (KBr) 3195, 2955, 1733, 1636, 1214, 720  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 507.8 ( $\text{C}_{13}\text{H}_{18}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 505.8 ( $\text{C}_{13}\text{H}_{18}^{35}\text{Cl}_6\text{N}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 126.0 (100%), 84.1. HR-MS calcd. for  $\text{C}_{13}\text{H}_{18}^{35}\text{Cl}_6\text{N}_3\text{O}_5$  ( $[\text{M}+\text{H}]^+$ ) 505.9377, found. 505.9399.

#### **Bis(2,2,2-trichloroethyl) 1-{1-(*t*-butoxycarbonyl)pyrrolidin-2-yl}hydrazine-1,2-dicarboxylate (41b)**

**40b** (0.185 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 15 : 1 *v/v*) gave **41b** (0.355 g, 62%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.46 (s, 9H), 1.50~1.65 (br, 3H), 1.63~1.77 (br, 1H), 1.79~1.94 (br, 1H), 2.05~2.20 (br, 1H), 3.10~3.32 (br, 1H), 3.75~3.95 (br, 1H), 4.52~5.10 (m, 4H), 5.75~6.00 (br, 1H), 6.75~7.00 (br, 1H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  18.00~19.10 (br), 23.18, 23.33, 27.41, 27.70, 28.21, 66.09, 66.09~67.40 (br), 74.81, 75.17, 75.36, 80.67, 94.42, 94.75, 153.00, 154.29, 154.61, 154.71, 154.92. IR (KBr) 3279, 2954, 1775, 1736, 1703, 1683, 1418, 718  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 565.8 ( $\text{C}_{16}\text{H}_{24}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 563.7 ( $\text{C}_{16}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 128.0 (100%). HR-MS calcd. for  $\text{C}_{16}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 563.9796, found. 563.9775.

#### **Bis(2,2,2-trichloroethyl) 1-(4-acetylmorpholin-3-yl)hydrazine-1,2-dicarboxylate (41g)**

**40g** (0.129 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and

stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 1 : 1 *v/v*) gave **41g** (0.0827 g, 16%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 2.04~2.38 (m, 3H), 3.20~3.40 (br, 1H), 3.45~3.65 (m, 1H), 3.70~3.85 (m, 1H), 3.90~4.10 (m, 1H), 4.10~4.50 (m, 1H), 4.55~5.00 (m, 4H), 5.70~6.20 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 20.50~22.50 (br), 38.56, 38.99, 42.67, 43.56, 64.16, 64.50, 65.54, 65.85, 66.53, 68.66, 70.32, 70.58, 74.94, 75.51, 94.52, 94.89, 151.00~155.00 (br), 171.00~173.00 (br). IR (KBr) 3208, 2967, 1732, 1651, 1274, 721 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 509.8 (C<sub>12</sub>H<sub>16</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>) (100%), 507.8 (C<sub>12</sub>H<sub>15</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>). HR-MS calcd. for C<sub>12</sub>H<sub>15</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 507.9170, found. 507.9147.

#### **Bis(2,2,2-trichloroethyl) 1-{4-(*t*-butoxycarbonyl)morpholin-3-yl}hydrazine-1,2-dicarboxylate (**41h**)**

**40h** (0.187 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **41h** (0.0702 g, 12%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.48 (s, 9H), 3.30~3.60 (m, 1H), 3.70~3.80 (m, 1H), 3.85~4.26 (m, 1H), 4.25~4.40 (m, 1H), 4.50~5.10 (m, 4H), 5.75~6.10 (m, 1H), 6.75~7.14 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.20, 39.89, 40.80, 62.00~64.00 (br), 65.85, 75.01, 75.51, 81.64, 94.74, 152.00~155.50 (br). IR (KBr) 3278, 2979, 1776, 1735, 1712, 721 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 567.8 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>7</sub>: [M+H]<sup>+</sup>), 565.8 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>7</sub>: [M+H]<sup>+</sup>), 511.8, 467.8, 186.0, 130.0 (100%), 86.0. HR-MS calcd. for C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>7</sub> ([M+H]<sup>+</sup>) 565.9589, found. 565.9601.

#### **Bis(2,2,2-trichloroethyl) 1-(4-acetylazepan-2-yl)hydrazine-1,2-dicarboxylate (**41c**)**

**40c** (0.141 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 2 : 1 *v/v*) gave **41c** (0.425 g, 81%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.15~1.54 (m, 3H), 1.68~2.02 (m, 3H), 2.07~2.40 (br, 1H), 2.16 (s, 3H), 2.70~3.00 (m, 0.4H), 3.40~3.68 (br, 1H), 4.25~4.37 (m, 0.4H), 4.50~5.13 (m, 4H), 5.72~6.04 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 21.66, 22.03, 23.86, 28.89, 29.10, 29.51, 30.16, 31.14, 31.40, 41.75, 42.04, 42.17, 44.75~47.00 (br), 69.20, 70.00~73.43 (br), 71.46, 74.68, 74.78, 75.16, 75.46, 94.76, 95.07, 152.77, 154.97, 172.09, 172.55. IR (KBr) 3194, 2930, 1730, 1638, 1205, 719 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 521.8 (C<sub>14</sub>H<sub>20</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 519.8 (C<sub>14</sub>H<sub>20</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 140.0 (100%), 98.0. HR-MS calcd. for C<sub>14</sub>H<sub>20</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 519.9534, found. 519.9508.

**Bis(2,2,2-trichloroethyl) 1-{1-(*t*-butoxycarbonyl)azepan-2-yl}hydrazine-1,2-dicarboxylate (41d)**

**40d** (0.199 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 6 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **41d** (0.542 g, 93%).

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.68~1.90 (br, 1H), 1.68~2.02 (m, 3H), 2.07~2.40 (br, 1H), 2.16 (s, 3H), 2.70~3.00 (m, 0.4H), 3.40~3.68 (br, 1H), 4.25~4.37 (m, 0.4H), 4.50~5.13 (m, 4H), 5.72~6.04 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 21.66, 22.03, 23.86, 28.89, 29.10, 29.51, 30.16, 31.14, 31.40, 41.75, 42.04, 42.17, 44.75~47.00 (br), 69.20, 70.00~73.43 (br), 71.46, 74.68, 74.78, 75.16, 75.46, 94.76, 95.07, 152.77, 154.97, 172.09, 172.55. IR (KBr) 3194, 2930, 1730, 1638, 1205, 719 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 579.8 (C<sub>17</sub>H<sub>26</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 577.9 (C<sub>20</sub>H<sub>26</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 523.8, 479.8, 198.1, 142 (100%). HR-MS calcd. for C<sub>17</sub>H<sub>26</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 577.9953, found. 577.9949.

**Bis(2,2,2-trichloroethyl) 1-[1-{*t*-butoxycarbonyl(butyl)amino}butyl]hydrazine-1,2-dicarboxylate (41e)**

**40e** (0.230 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **41e** (0.335 g, 55%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.919 (t, *J* = 7.6 Hz, 3H), 0.90~1.00 (br, 3H), 1.27 (quint, *J* = 7.6 Hz, 4H), 1.33~1.50 (m, 2H), 1.47 (s, 9H), 1.75~2.10 (br, 2H), 3.10~3.34 (br, 2H), 4.50~5.10 (m, 4H), 5.15~5.50 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 13.66, 18.86, 19.99, 28.20, 31.49, 31.70~33.90 (br), 43.00~52.00 (br), 71.70~74.70 (br), 74.67, 75.31, 80.38, 153.50, 153.73, 155.29. IR (KBr) 3287, 2961, 1736, 1679, 1155, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 609.8 (C<sub>19</sub>H<sub>32</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 607.8 (C<sub>19</sub>H<sub>32</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 553.8, 507.9, 436.7, 228.1, 172.0 (100%), 128.1. HR-MS calcd. for C<sub>19</sub>H<sub>32</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 608.0422, found. 608.0437.

**Bis(2,2,2-trichloroethyl) 1-[[benzyl(*t*-butoxycarbonyl)amino](phenyl)methyl]hydrazine-1,2-dicarboxylate (41f)**

**40f** (0.298 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **41f** (0.0844 g, 12%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.37~1.51 (br, 9H), 4.30~5.00 (m, 7H), 7.06~7.44 (m, 10H). <sup>13</sup>CNMR (100

MHz, CDCl<sub>3</sub>)  $\delta$  28.24, 51.00~55.00 (br), 74.58, 75.66, 81.59, 84.66, 94.78, 127.28, 127.63, 128.29, 128.67, 133.00~134.50 (br), 137.00~138.50 (br), 152.50~154.60 (br), 155.00~156.00 (br). IR (KBr) 3299, 2977, 1772, 1731, 1682, 736, 716, 700 cm<sup>-1</sup>. FABMS (NBA)  $m/z$ : 677.9 (C<sub>25</sub>H<sub>28</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 675.9 (C<sub>25</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 470.8, 296.1, 240.0 (100%), 196.1. HR-MS calcd. for C<sub>25</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 676.0109, found. 676.0110.

#### **Bis(2,2,2-trichloroethyl) 1-(acetylidolin-2-yl)hydrazine-1,2-dicarboxylate (41i)**

**40i** (0.161 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 5 : 1 *v/v*) gave **41i** (0.109 g, 24%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.57 (s, 3H), 2.15~2.55 (m, 4H), 4.35~5.15 (m, 6H), 6.50~6.75 (m, 1H), 6.95~7.07 (m, 1H), 7.07~7.23 (m, 2H), 8.00~8.15 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  23.35, 34.18, 72.44, 74.60, 74.90, 75.46, 75.78, 94.72, 94.83, 116.69, 124.29, 124.50, 127.51, 129.00, 142.00, 152.91, 155.06, 171.20. IR (KBr) 3181, 2982, 1768, 1733, 1650, 754, 725 cm<sup>-1</sup>. FABMS (NBA)  $m/z$ : 541.8 (C<sub>16</sub>H<sub>16</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 539.8 (C<sub>16</sub>H<sub>16</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 232.1, 176.0 (100%). HR-MS calcd. for C<sub>16</sub>H<sub>16</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 539.9221, found. 539.9218.

#### **Bis(2,2,2-trichloroethyl) 1-{1-(*t*-butoxycarbonyl)indolin-2-yl}hydrazine-1,2-dicarboxylate (41j)**

**40j** (0.219 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 30 : 1 *v/v*) gave **41j** (0.353 g, 59%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  1.53~1.62 (m, 11H), 3.30~3.71 (m, 2H), 4.40~4.25 (m, 4H), 6.50~6.80 (m, 1H), 6.87~7.03 (m, 1H), 7.05~7.20 (m, 2H), 7.55~7.75 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  28.24, 32.61, 32.75, 33.74, 71.28, 71.62, 74.81, 74.98, 75.44, 75.71, 82.29, 94.52, 94.61, 122.82, 124.04, 127.34, 128.12, 128.40, 141.47, 151.73, 152.00, 152.16, 152.75, 153.96, 154.40. IR (KBr) 3293, 2980, 1740, 1716, 749, 724 cm<sup>-1</sup>. FABMS (NBA)  $m/z$ : 598.8 (C<sub>19</sub>H<sub>22</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>) (100%), 596.8 (C<sub>19</sub>H<sub>22</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 543.8, 499.8, 218.0, 162.0, 117.9 (100%). HR-MS calcd. for C<sub>19</sub>H<sub>22</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 597.9640 found. 597.9652.

#### **Bis(2,2,2-trichloroethyl) 1-(acetyl-1,2,3,4-tetrahydroquinolin-2(1*H*)-yl)hydrazine-1,2-dicarboxylate (41k)**

**40k** (0.176 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and

stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 4 : 1 *v/v*) gave **41k** (0.0983 g, 18%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.73~0.97 (m, 1H), 1.00~1.40 (m, 2H), 2.07~2.34 (m, 3H), 2.34~2.80 (m, 2H), 4.28~5.00 (m, 4H), 6.35~6.65 (m, 1H), 6.90~7.30 (m, 4H), <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 23.00, 25.60, 29.61, 67.50~68.50 (br), 74.84, 75.57, 94.70, 125.34, 126.20, 126.90, 127.07, 133.70~136.20 (br), 137.50~139.00 (br), 151.60~155.30 (br), 171.81. IR (KBr) 3294, 2923, 1736, 1652, 1204, 751, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 555.8 (C<sub>17</sub>H<sub>18</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 553.8 (C<sub>17</sub>H<sub>18</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 174.0 (100%), 132.0. HR-MS calcd. for C<sub>17</sub>H<sub>18</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 553.9377, found. 553.9360.

#### **Bis(2,2,2-trichloroethyl) 1-{1-(*t*-butoxycarbonyl)-1,2,3,4-tetrahydroquinolin-2(1*H*)-yl}hydrazine-1,2-dicarboxylate (41l)**

**40l** (0.233 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **41l** (0.358 g, 58%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.12~1.40 (m, 2H), 1.80~2.10 (br, 1H), 2.20 (s, 3H), 2.40~2.80 (m, 2H), 4.30~5.00 (m, 4H), 6.30~6.65 (br, 1H), 6.95~7.30 (br, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 23.00, 25.60, 29.61, 67.50~69.00 (br), 74.84, 75.57, 125.34, 126.20, 126.90, 127.07, 133.00~137.30 (br), 137.50~139.00 (br), 151.00~153.00 (br), 171.81. IR (KBr) 3290, 2979, 1775, 1734, 752, 717 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 613.8 (C<sub>20</sub>H<sub>24</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 611.8 (C<sub>20</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 557.8, 513.8, 232.1, 176.0, 132.0 (100%). HR-MS calcd. for C<sub>20</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 611.9796, found. 611.9784.

#### **Bis(2,2,2-trichloroethyl) 1-(5-oxopyrrolidin-2-yl)hydrazine-1,2-dicarboxylate (41m)**

**40m** (0.0851 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*) gave **41m** (0.150 g, 32%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.55~1.67 (m, 1H), 2.23~2.40 (m, 1H), 2.40~2.60 (m, 2H), 4.55~5.05 (4H), 5.90~6.10 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 23.91, 24.25, 28.70~29.80 (br), 68.57, 68.70~69.80 (br), 74.89, 75.54, 75.75, 94.41, 94.64, 94.87, 153.12, 154.96, 180.02, 180.24. IR (KBr) 3223, 2959, 1731, 1697, 1416, 721 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 465.8 (C<sub>10</sub>H<sub>12</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 463.8 (C<sub>10</sub>H<sub>12</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 84.1 (100%), 77.1. HR-MS calcd. for C<sub>10</sub>H<sub>12</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 463.8908,

found. 463.8921.

**Bis(2,2,2-trichloroethyl) 1-(6-oxopiperidin-2-yl)hydrazine-1,2-dicarboxylate (41n)**

**40n** (0.0992 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After stirred to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 1 : 1 *v/v*) gave **41n** (0.121 g, 25%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.70~2.23 (m, 4H), 2.27~2.47 (m, 2H), 4.60~4.98 (m, 4H), 5.67~5.90 (br, 1H), 6.13~6.39 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 17.97, 24.99, 25.33, 29.59, 30.78, 65.65, 66.75, 74.96, 75.71, 94.44, 94.62, 94.87, 153.43, 154.20~155.70 (br), 173.83. IR (KBr) 3210, 2958, 1734, 1661, 1394, 717 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 479.8 (C<sub>11</sub>H<sub>14</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 477.8 (C<sub>11</sub>H<sub>14</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>), 98.0 (100%). HR-MS calcd. for C<sub>11</sub>H<sub>13</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 477.9064, found. 477.9068.

**Bis(2,2,2-trichloroethyl) 1-(7-oxoazepan-2-yl)hydrazine-1,2-dicarboxylate (41o)**

**40o** (0.133 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 1 : 1 *v/v*) gave **41o** (0.0512 g, 10%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.40~1.95 (m, 4H), 2.00~2.35 (m, 2H), 2.35~2.60 (m, 2H), 4.62~5.00 (m, 4H), 5.60~5.75 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 22.46, 27.56, 32.49, 36.58, 67.00~69.50 (br), 75.04, 75.80, 153.13, 154.58, 177.75. IR (KBr) 3322, 2933, 1772, 1732, 1660, 714 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 493.8 (C<sub>12</sub>H<sub>16</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>) (100%), 491.8 (C<sub>12</sub>H<sub>16</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub>: [M+H]<sup>+</sup>). HR-MS calcd. for C<sub>12</sub>H<sub>16</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>5</sub> ([M+H]<sup>+</sup>) 491.9221, found. 491.9221.

**Bis(2,2,2-trichloroethyl) 1-(2-acetyl-1,2,3,4-tetrahydroisoquinolin-1(2H)-yl)hydrazine-1,2-dicarboxylate (43a)**

**42a** (0.176 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 3 : 1 *v/v*) gave **43a** (0.477 g, 86%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 2.25 (s, 1.5H), 2.38 (s, 1.5H), 2.75~2.95 (m, 2H), 3.05~3.25 (br, 0.35H), 3.60~4.00 (m, 1H), 4.54~5.18 (m, 4H), 6.50~6.80 (m, 1H), 6.90~7.45 (m, 4H), 7.50~7.75 (m, 0.31H), 7.80~8.00 (m, 0.35H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 21.95, 22.46, 28.51, 28.80~31.00 (br), 36.20~38.40 (br), 41.30~43.80 (br), 64.50~70.00 (br), 74.81, 75.03, 75.51, 126.40, 126.90, 127.16, 127.34, 128.24,

128.79, 128.98, 129.25, 130.20, 130.98, 136.72, 136.85, 152.00~153.60 (br), 170.80~172.00 (br). IR (KBr) 3125, 2955, 1741, 1643, 1402, 743, 709  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 555.8 ( $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 553.8 ( $\text{C}_{17}\text{H}_{18}^{35}\text{Cl}_6\text{N}_3\text{O}_5$ :  $[\text{M}+\text{H}]^+$ ), 174.0 (100%), 132.0. HR-MS calcd. for  $\text{C}_{12}\text{H}_{15}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 553.9377, found. 553.9370.

**Bis(2,2,2-trichloroethyl) 1-{2-(*t*-butoxycarbonyl)-1,2,3,4-tetrahydroisoquinolin-1(2*H*)-yl}hydrazine-1,2-dicarboxylate (43b)**

**42b** (0.233 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 3 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **43b** (0.589 g, 96%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.44~1.59 (m, 9H), 2.81 (s, 2H), 3.14~3.34 (br, 0.5H), 3.37~3.57 (br, 0.5H), 4.05~4.25 (br, 0.5H), 4.28~4.45 (m, 0.5H), 4.50~5.15 (m, 4H), 6.45~6.75 (m, 1H), 7.00~7.50 (m, 4H), 7.55~7.80 (m, 1H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.29, 28.87, 38.21, 39.94, 66.00~67.00 (br), 68.00~69.50 (br), 74.65, 74.93, 75.34, 75.58, 80.90, 81.25, 94.67, 94.76, 126.89, 128.24, 128.76, 129.25, 131.43, 135.49, 136.45, 153.28, 153.73, 154.29. IR (KBr) 3281, 2979, 1782, 1735, 1707, 1415, 748, 722  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 613.8 ( $\text{C}_{20}\text{H}_{24}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 611.8 ( $\text{C}_{20}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 539.8, 511.8, 232.1, 176.0 (100%). HR-MS calcd. for  $\text{C}_{20}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 611.9796, found. 611.9797.

**Bis(2,2,2-trichloroethyl) 1-{1-(benzyloxycarbonyl)-1,2,5,6-tetrahydropyridin-2(1*H*)-yl}hydrazine-1,2-dicarboxylate (43c)**

**42c** (0.219 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **43c** (0.445 g, 74%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.00~2.28 (m, 2H), 3.04~3.26 (br, 1H), 4.20~4.40 (br, 1H), 4.45~5.00 (m, 4H), 5.05~5.30 (m, 2H), 5.75~5.95 (br, 1H), 6.05~6.55 (m, 2H), 7.29~7.45 (m, 5H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  24.06, 37.00~40.00 (br), 63.00~65.00 (br), 67.00~68.50 (br), 74.50~76.00 (br), 94.94, 122.00~123.50 (br), 128.19, 128.47, 129.50~130.50 (br), 135.00~136.50 (br), 152.00~153.00 (br), 153.50~155.00 (br), 155.32. FABMS (NBA)  $m/z$ : 597.8 ( $\text{C}_{19}\text{H}_{20}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 595.8 ( $\text{C}_{19}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 551.8, 489.8, 216.0 (100%), 172.0, 91.0. HR-MS calcd. for  $\text{C}_{19}\text{H}_{20}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 595.9483, found. 595.9496.

**Bis(2,2,2-trichloroethyl) 1-[1-{*t*-butoxycarbonyl(ethyl)amino}allyl]hydrazine-1,2-dicarboxylate (43d)**

**42d** (0.185 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **43d** (0.120 g, 21%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.13 (t, *J* = 7.2 Hz, 3H), 1.47 (s, 9H), 3.20~3.60 (m, 2H), 4.65~5.00 (m, 4H), 5.25~5.45 (m, 2H), 5.55~5.90 (br, 1H), 5.95~6.20 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 14.47, 28.31, 45.10, 74.83, 75.49, 80.72, 94.78, 94.93, 119.93, 120.34, 129.87, 153.38, 153.79, 154.96. IR (KBr) 3287, 2957, 1733, 1423, 1134, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 595.9 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 593.9 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 463.8, 420.8, 184.1, 128.0 (100%). HR-MS calcd. for C<sub>19</sub>H<sub>20</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 595.9483, found. 595.9496.

**Bis(2,2,2-trichloroethyl) 1-[1-{*t*-butoxycarbonyl(ethyl)amino}prop-2-ynyl]hydrazine-1,2-dicarboxylate (43e)**

**42e** (0.184 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 20 : 1 *v/v*) gave **43e** (0.286 g, 51%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.14~1.24 (m, 3H), 1.48 (s, 9H), 2.50~2.75 (br, 1H), 3.25~3.75 (m, 2H), 4.64~5.00 (m, 4H), 6.15~6.50 (br, 1H), 6.60~7.15 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 14.40, 28.24, 40.80, 42.30~45.00 (br), 60.50~66.00 (br), 71.40, 74.99, 75.24, 75.37, 75.61, 75.83, 76.15, 81.46, 94.54, 94.74, 152.58, 153.78. IR (KBr) 3289, 2977, 1735, 1153, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 565.9 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 563.9 (C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 463.8, 420.8, 184.1, 128.0 (100%). HR-MS calcd. for C<sub>16</sub>H<sub>24</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 563.9796, found. 563.9796.

**Bis(2,2,2-trichloroethyl) 1-[1-{*t*-butoxycarbonyl(methyl)amino}(phenyl)methyl]hydrazine-1,2-dicarboxylate (43f)**

**42f** (0.221 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : Et<sub>2</sub>O = 5 : 1 *v/v*) gave **43f** (0.156 g, 26%), and **44f** (0.0696 g, 11%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.50 (s, 9H), 2.66~2.96 (br, 2H), 4.52~4.94 (m, 4H), 5.50~5.70 (m, 1H), 6.30~6.60 (br, 1H), 7.27~7.47 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 14.91, 17.60~19.00 (br), 28.29,

31.50~34.00 (br), 34.5~36.20 (br), 63.00~64.50 (br), 74.64, 75.09, 75.63, 81.15, 94.68, 94.75, 125.80~127.30 (br), 127.70, 127.81, 128.48, 128.58, 132.80~135.00 (br), 153.72, 155.78. IR (KBr) 3282, 2978, 1778, 1737, 1683, 1148, 718  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 601.8 ( $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 599.8 ( $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 470.8, 220.1, 164.0 (100%), 120.0. HR-MS calcd. for  $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 599.9796, found. 599.9782.

**Bis(2,2,2-trichloroethyl) 1-[{benzyl(*t*-butoxycarbonyl)amino}methyl]hydrazine-1,2-dicarboxylate (44f)**

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.54 (br, 9H), 4.50~4.60 (br, 2H), 4.65~4.90 (br, 4H), 4.95~5.20 (m, 1H), 7.10~7.45 (m, 5H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  28.25, 48.00~51.00 (br), 60.00~63.00 (br), 75.07, 75.59, 81.22, 127.49, 128.62, 138.14, 152.00~157.00 (br). IR (KBr) 3278, 2978, 1735, 1703, 1681, 1153, 726  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 601.8 ( $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 599.8 ( $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 545.8, 501.9, 220.1, 120.0 (100%). HR-MS calcd. for  $\text{C}_{19}\text{H}_{24}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 599.9796, found. 599.9772.

**Bis(2,2,2-trichloroethyl) 1-[1-{benzyl(*t*-butoxycarbonyl)amino}ethyl]hydrazine-1,2-dicarboxylate (44g)**

**42g** (0.236 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **44g** (0.259 g, 41%) as colorless crystals.

$^1\text{H}$ NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  0.80~1.10 (m, 3H), 1.27~1.36 (br, 3H), 1.47 (s, 5H), 1.50 (s, 4H), 3.22~3.42 (br, 1H), 4.20~4.37 (m, 1H), 4.44~5.10 (m, 4H), 5.35~5.85 (br, 1H), 6.30~6.50 (m, 1H), 7.20~7.48 (m, 5H).  $^{13}\text{C}$ NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  14.20, 15.00~17.00 (br), 28.29, 44.00~45.50 (br), 55.05~55.00 (br), 68.50~71.00 (br), 74.45, 74.81, 74.97, 75.56, 76.18, 80.91, 81.15, 94.68, 94.75, 94.80, 94.88, 127.38, 127.95, 128.14, 128.30, 128.40, 128.58, 133.00~135.00 (br), 138.25, 153.20, 153.74, 153.98, 155.00, 155.60. IR (KBr) 3295, 2978, 1773, 1735, 1682, 1154, 716  $\text{cm}^{-1}$ . FABMS (NBA)  $m/z$ : 615.8 ( $\text{C}_{20}\text{H}_{26}^{35}\text{Cl}_5^{37}\text{ClN}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 613.8 ( $\text{C}_{20}\text{H}_{26}^{35}\text{Cl}_6\text{N}_3\text{O}_6$ :  $[\text{M}+\text{H}]^+$ ), 559.8, 513.9, 470.8, 408.8, 234.1, 178.0 (100%), 134.1. HR-MS calcd. for  $\text{C}_{20}\text{H}_{26}^{35}\text{Cl}_6\text{N}_3\text{O}_6$  ( $[\text{M}+\text{H}]^+$ ) 613.9953, found. 613.9949.

**Bis(2,2,2-trichloroethyl) 1-[{*t*-butoxycarbonyl(propyl)amino}(phenyl)methyl]hydrazine-1,2-dicarboxylate (43h)**

**42h** (0.249 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced

pressure. Purification by column chromatography (*n*-hexane : EtOAc = 15 : 1 *v/v*) gave **43h** (0.106 g, 17%), and **44h** (0.130 g, 21%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.70~0.85 (m, 3H), 1.35~1.57 (m, 11H), 3.10~3.40 (m, 2H), 4.40~5.00 (m, 4H), 6.22~6.52 (m, 1H), 7.15~7.55 (m, 5H), 7.80~8.30 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 11.26, 22.12, 22.26, 28.29, 51.50~52.40 (br), 74.44, 74.98, 75.45, 75.59, 80.91, 94.76, 94.83, 128.08, 128.30, 128.41, 128.51, 128.79, 133.00~135.00 (br), 153.26, 153.80, 153.91, 155.80. IR (KBr) 3372, 2972, 1774, 1736, 1683, 1151, 717 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 629.8 (C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 627.8 (C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 470.8, 248.1, 192.1 (100%). HR-MS calcd. for C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 628.0109, found. 628.0100.

**Bis(2,2,2-trichloroethyl) 1-[1-{benzyl(*t*-butoxycarbonyl)amino}propyl]hydrazine-1,2-dicarboxylate (44h)**

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 0.65~1.00 (br, 3H), 1.30~1.60 (m, 9H), 1.70~2.00 (m, 2H), 4.15~5.45 (m, 2H), 4.52~5.00 (m, 5H), 5.50~5.80 (m, 1H), 7.25~7.40 (m, 5H), 7.50~7.60 (br, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 9.94, 22.45, 28.24, 47.00~53.00 (br), 72.70~74.00 (br), 74.86, 75.48, 81.18, 127.32, 128.58, 138.66, 153.54, 153.89, 155.49. IR (KBr) 3291, 2976, 1775, 1736, 1701, 1157, 718 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 629.9 (C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 627.9 (C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 573.8, 529.8, 422.8, 248.1, 192.1 (100%). HR-MS calcd. for C<sub>21</sub>H<sub>28</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 628.0109, found. 628.0107.

**Bis(2,2,2-trichloroethyl) 1-[{allyl(*t*-butoxycarbonyl)amino}(phenyl)methyl]hydrazine-1,2-dicarboxylate (43i)**

**42i** (0.247 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 10 : 1 *v/v*) gave **43i** (0.411 g, 60%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.32~1.52 (m, 9H), 3.40~3.64 (br, 1H), 4.20~5.05 (m, 6H), 5.68~5.90 (m, 1H), 7.20~7.40 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.09, 47.50~52.50 (br), 75.00, 75.62, 81.68, 127.28, 128.48, 138.38, 152.88, 154.54. IR (KBr) 3377, 2978, 1736, 1689, 1160, 719 cm<sup>-1</sup>. FABMS (NBA) *m/z*: 597.8 (C<sub>21</sub>H<sub>25</sub><sup>35</sup>Cl<sub>5</sub><sup>37</sup>ClN<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 595.8 (C<sub>19</sub>H<sub>20</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub>: [M+H]<sup>+</sup>), 551.8, 489.8, 216.0 (100%), 172.0, 91.0. HR-MS calcd. for C<sub>19</sub>H<sub>20</sub><sup>35</sup>Cl<sub>6</sub>N<sub>3</sub>O<sub>6</sub> ([M+H]<sup>+</sup>) 595.9483, found. 595.9496.

**Bis(2,2,2-trichloroethyl) 1-[{*t*-butoxycarbonyl(prop-2-ynyl)amino}(phenyl)methyl]hydrazine-1,2-dicarboxylate (43j)**

**42j** (0.245 g, 1.0 mmol) was dissolved in benzene (3.3 mL), **23e** (0.457 g, 1.2 mmol) was added, and

stirred at reflux for 12 h. After cooled to room temperature, the solvent was removed under reduced pressure. Purification by column chromatography (*n*-hexane : EtOAc = 15 : 1 *v/v*) gave **43j** (0.143 g, 23%) and **44j** (0.123 g, 20%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.41 (s, 9H), 1.60~1.80 (br, 1H), 4.35~5.05 (m, 6H), 5.68~5.90 (m, 1H), 6.95~7.05 (m, 1H), 7.10~7.40 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.11, 30.50~32.00 (br), 75.10, 75.64, 76.22, 82.00, 94.23, 94.61, 126.80, 127.30, 128.57, 138.00~139.50 (br), 151.88~154.70 (br).

**Bis(2,2,2-trichloroethyl) 1-[1-{benzyl(*t*-butoxycarbonyl)amino}prop-2-ynyl]hydrazine-1,2-dicarboxylate (**44j**)**

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.16~1.58 (br, 9H), 2.46~2.78 (m, 1H), 4.35~4.50 (m, 2H), 4.60~5.10 (m, 4H), 7.20~7.40 (m, 5H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 28.10, 48.00~53.00 (br), 61.00~66.00 (br), 74.72, 74.97, 75.68, 76.52, 82.04, 94.23, 94.61, 126.59, 126.59, 126.83, 127.34, 128.16, 137.91, 152.53, 153.68, 154.40.

**Reaction of alpha-oxidation product 26e with nucleophile in the presence of Lewis acid catalyst**

**26e** (0.494 g, 1.00 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9 mL), and 1.0 M CH<sub>2</sub>Cl<sub>2</sub> solution of TiCl<sub>4</sub> (0.5 mL, 0.50 mmol) was added dropwise at room temperature. After reflux for 24 h, the mixture was cooled to room temperature, and cooled on ice. Saturated aqueous NaHCO<sub>3</sub> solution was added, and the mixture was filtered through Celite. Filtrate and washings (CH<sub>2</sub>Cl<sub>2</sub>) were combined and washed with saturated aqueous NaHCO<sub>3</sub> solution. Organic layer was dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 2 : 1 *v/v*) gave **45** (0.123 g, 88%) as colorless liquid.

**1-(2-Allylpyrrolidin-1-yl)ethan-1-one (**45**)**

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.72~2.25 (m, 7H), 2.28~2.35, 2.52~2.63 (m, 2H), 3.35~3.60 (m, 2H), 3.80~3.90 (m, 1H), 4.10~4.20 (m, 1H), 5.00~5.15 (m, 2H), 5.67~5.83 (m, 1H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 22.72, 23.53, 28.30, 37.05, 45.21, 57.75, 116.78, 117.78, 133.75, 134.84, 168.70, 168.76. IR (KBr) 2973, 1634, 1419 cm<sup>-1</sup>.

**4,4-Dimethylhexahydro-1H-pyrrolo[1,2-c][1,3]oxazin-1-one (**47**)**

**39e** (0.552 g, 1.00 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9 mL), and cooled on ice. 1.0 M CH<sub>2</sub>Cl<sub>2</sub> solution of TFMSA, (1.2 mL, 1.20 mmol) was added, and stirred at 4 °C for 3 h, and then at room temperature for 1 h. After cooled on ice, the reaction was quenched by adding saturated aqueous NaHCO<sub>3</sub> solution, and layers were separated. Organic layer was washed twice with saturated aqueous NaHCO<sub>3</sub> solution, dried over

anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 5 : 1 v/v) gave **47** (0.0607 g, 36%) as colorless crystals.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.34~1.52 (m, 2H), 1.38 (s, 3H), 1.43 (s, 3H), 1.75~1.89 (m, 1H), 1.97~2.08 (m, 2H), 2.14 (quint, *J* = 6.0 Hz, 1H), 3.45~3.65 (m, 3H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 22.65, 25.51, 29.50, 33.08, 38.93, 46.15, 53.54, 78.36, 152.75. IR (KBr) 3280, 1755, 1714, 1221 cm<sup>-1</sup>.

**Mixture of (3*S*\*,4*aS*\*)-3-(4-Chlorophenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (48a) and (3*R*\*,4*aS*\*)-3-(4-Chlorophenyl)hexahydro-1*H*-pyrrolo[1,2-*c*][1,3]oxazin-1-one (48b)**

**39e** (0.552 g, 1.00 mmol) was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (9 mL), and *p*-chlorostyrene (0.24 mL, 2.00 mmol) was added. After cooled on ice, a solution of TiCl<sub>4</sub> (2.0 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.5 mL, 3.00 mmol) was added, and CO<sub>2</sub> gas was bubbled into the reaction mixture for 1 h. After stirred at 4 °C for 2 h, the mixture was stirred at room temperature for 1 h. After cooled on ice, the reaction was quenched by adding saturated aqueous NaHCO<sub>3</sub> solution, and the mixture was filtered through Celite. The filtrate was washed twice with saturated aqueous NaHCO<sub>3</sub> solution, dried over anhydrous magnesium sulfate, and evaporated. Purification by column chromatography (*n*-hexane : EtOAc = 5 : 1 v/v) gave mixture of **48a** and **48b** (0.0514 g, 3.7 : 1, 20%) as white solid.

<sup>1</sup>HNMR (400 MHz, CDCl<sub>3</sub>) δ 1.40~1.78 (m, 2.4H), 1.75~2.15 (m, 3.2H), 2.20 (quint, *J* = 6.0 Hz, 1H), 2.35~2.44 (m, 1.4H), 3.08~3.20 (m, 0.4H), 3.46~3.76 (m, 4.2H), 5.24 (dd, *J* = 2.4, 11.6 Hz, 1H), 5.48~5.62 (m, 0.4H), 7.19~7.38 (m, 5.6H). <sup>13</sup>CNMR (100 MHz, CDCl<sub>3</sub>) δ 22.52, 22.92, 32.99, 33.13, 33.61, 36.36, 46.51, 46.81, 51.86, 56.53, 76.30, 77.91, 126.14, 127.14, 128.69, 128.76, 133.51, 134.04, 137.60, 138.30, 152.32, 152.68. IR (KBr) 2972, 1683, 1125 cm<sup>-1</sup>. EIMS *m/z*: 251 (M<sup>+</sup>), 206, 138 (100%). HR-MS calcd. for C<sub>13</sub>H<sub>14</sub><sup>35</sup>ClNO<sub>2</sub> (M<sup>+</sup>) 251.0713, found. 251.0701.

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