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Studies on Lewis Acid-Promoted Cyclization Reactions
Utilizing Allenes

Yugo Fukushima

February 2014

Doctoral Thesis at Osaka Prefecture University
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Chapter 1

General Introduction

The development of new efficient bond-forming reactions is of great importance in synthetic organic chemistry. Utilization of atypical compounds may provide valuable synthetic methodologies.

In 1887 Burton and Pechmann prepared the first allenic compound, and its structure was confirmed in 1954. Because of the belief that cumulated systems would be thermally unstable, their chemistry and synthetic applications had not been well established. The first natural product including an allene structure was isolated in 1924. Now it is known that allenes are present in many natural products. Owing to the presence of the unique cumulated diene structural unit, allenes have been recognized as promising components to realize various synthetic transformations.

The electron density and the reactivity of each carbon atom of the allene unit can be tuned by the substituent effect. Allenes can react as both nucleophiles and electrophiles and would give the diverse products with region- and stereoselectively, depending on the substituents and catalysts (Scheme 1-1). Owing to the high degree of unsaturation, methodologies starting from allenes would make the products amenable to further functionalizations.
Recently, significant advances in allene chemistry are in progress. Among the synthetic reactions using allenes, transition metal-catalyzed reactions leading to a variety of products have been studied extensively.\(^6\) Thermal,\(^7\) photochemical,\(^8\) reductive\(^9\) and base-promoted\(^{10}\) reactions of allenes have also been reported. Lewis acids play a major role in carbon-carbon bond-forming processes by coordinating to carbonyl compounds.\(^{11}\) However, the Lewis acid-mediated reactions of allenes have been less studied.\(^{12}\)

From these points of view, in this thesis, the investigations and detailed discussion on the Lewis acid-promoted cyclization reactions utilizing allenes to lead to synthetically useful heterocyclic and carbocyclic skeletons are presented.

This thesis is divided into five chapters. The introduction is presented in chapter 1. In chapter 2, Lewis acid-promoted addition/cyclization reaction of 1,1-diarylallenes and carbonyl compounds is described. Lewis acid-promoted reaction of arylallenes with ethenetricarboxylates or ketone derivatives has been examined. The reaction of arylallenes and ethenetricarboxylate derivatives with Lewis acids gave indene derivatives efficiently, via a conjugate addition/cyclization
reaction. The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate or triethyl ethenetricarboxylate and alkylallene with SnCl₄ gave γ-lactones. The reactions of triethyl ethenetricarboxylate and 1,1-dialkylallenes with SnCl₄ at room temperature also gave γ-lactones. SnCl₄-promoted reaction of diarylallenes with vinyl ketones gave indene derivatives via conjugate addition/cyclization reaction. The reaction of diphenylallene with diethyl ketomalonate in the presence of SnCl₄ at -40 °C gave hydroxyindenylmalonate as a major product via carbonyl addition/cyclization reaction. The reaction at 80 °C gave indenylmalonate. Chapter 3 deals with Lewis acid-promoted cyclization reactions of allenyl ethenetricarboxylates with the amides. Lewis acid-promoted intramolecular reactions of allenyl ethenetricarboxylates with the corresponding amides have been examined. Reaction of allenyl ethenetricarboxylates and the amides with Lewis acids such as AlCl₃, AlBr₃ and ZnX₂ (X = Cl, Br, I) gave 3,4-trans haloalkenyl five-membered heterocycles stereoselectively. The stereochemistry was determined by NOE experiments and reduction of the cyclized products. Various transformations of the haloalkenyl functionalized cyclic compounds have also been described. Chapter 4 deals with the cyclization reactions of substituted allenyl ethenetricarboxylates. The regioselectivity and stereoselectivity of the cyclization reactions of substituted allenyl ethenetricarboxylates have been investigated. The reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate with Lewis acids such as AlCl₃ and SnCl₄ gave a chlorine-incorporated six-membered oxygen-containing heterocycle selectively. Finally, the summary of this thesis is presented in chapter 5.
References

1 Burton, B. S.; Pechmann, H. V. Chem. Ber. 1887, 20, 145.


Chapter 2

Lewis Acid-Promoted Addition/Cyclization Reaction of 1,1-Diarylallenes with Carbonyl Compounds

2-1 Introduction

Allene derivatives play an important role in organic synthesis because of their structural features with two cumulated carbon-carbon double bonds. Exploring new synthetic reactions using allenes has attracted much attention. Few simple arylallenes have been used in Friedel-Crafts reaction. Recently, various Lewis acid-promoted reactions of ethenetricarboxylate derivatives have been studied and it has been reported that they function as highly electrophilic Michael acceptors. For example, the reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate (2e) and various alkenes in the presence of a Lewis acid gave cycloadducts, γ-lactones, (route a in Scheme 2-1). It has also been reported that the reaction of ethenetricarboxylate triester with chloroallenes, which were generated in situ by the reaction of γ-trifluoromethyl-R-aryl propargyl alcohols with SnCl₄, gave cyclobutane derivatives (route b). Simple arylallenes are expected to add to ethenetricarboxylates in the presence of Lewis acid and undergo further bond formation reaction on benzene ring via the common zwitter ionic intermediate A (route c). Therefore, Lewis acid-catalyzed reactions of ethenetricarboxylates with arylallenes and also alkylallenes for comparison have been examined.
2-2 Result and Discussion

The reaction of 1,1-diarylallenes 1a-c and ethenetricarboxylate triesters 2a-c with SnCl₄ at room temperature overnight gave indene derivatives 3 in 79-99% yield via conjugate addition/Friedel-Crafts cyclization reaction (eq. 2-1). In the reaction, the phenylallene moiety reacted with SnCl₄-coordinated ethenetricarboxylates 2 to form a phenyl allylic cation intermediates, followed by a cyclization.
The reaction of arylallene 1a with ethenetricarboxylate derivatives 2 in the presence of various Lewis acids such as AlCl₃, FeCl₃, and InBr₃ was examined.

The catalytic use (0.2 equivalent) of AlCl₃ was also effective for the indene formation by the reaction of 2a with 1a. The reaction of 1,1-diarylallene 1a and ethenetricarboxylate triester 2a with AlCl₃ (0.2 equivalent) at 80 °C overnight gave indene derivative 3a in 69% yield. Use of 0.2 equivalent of FeCl₃ and InBr₃ at room temperature or 80 °C gave the starting materials or complex mixtures.

In addition, the reaction of arylallenes 1a with ethenetricarboxylate analogue, diethyl 2-(cyanomethylene)malonate (2d), in the presence of SnCl₄ (1.0 equivalent) was examined. The reaction at room temperature gave the corresponding indene derivative 3 in 64% yield.

Lewis acid-catalyzed reactions of ethenetricarboxylates with alkylallenes for comparison have been examined. The reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (2e) with allenes 1 in the presence of SnCl₄ gave exomethylene γ-lactones 4 and/or the conjugated isomers, α,β-unsaturated-γ-lactones 5 after usual work-up (eq. 2-2). The exomethylene γ-lactones 4 are unstable to distillation or column chromatography and difficult to be purified. Treatment of γ-lactones
4 or the mixture of 4 and 5 with Et₃N gave γ-lactones 5.

\[
\begin{align*}
\text{EtO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} + \text{R}^1 & \text{R}^2 \quad \overset{\text{SnCl}_4 (1.0 \text{ equiv.})}{\longleftarrow} \quad \overset{\text{CH}_2\text{Cl}_2}{\text{-78 °C or rt}} \\
\text{HO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} & \text{EtO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} \\
\text{R}^1 & \text{R}^2 & \text{R}^1 & \text{R}^2 \\
\text{Et}_3\text{N} & \overset{\text{CH}_2\text{Cl}_2}{\text{rt 0.5 h}} & \text{Et}_3\text{N} & \text{EtO}_2\text{C} \\
\text{CH}_2\text{Cl}_2 & \text{rt 0.5 h} & \text{CH}_2\text{Cl}_2 & \text{rt 0.5 h}
\end{align*}
\]

(2-2)

The author prepared various alkyl allenes and showed that the reactions of 1,1-diethyl 2-hydrogen ethenetricarboxylate (2e) with 3-methyl-1,2-octadiene (1d) in the presence of one equivalent of SnCl₄ at room temperature gave γ-lactone 5a in 17% yield. The reactions of triethyl ethenetricarboxylate (2a) with alkylallene 1d in the presence of SnCl₄ at room temperature also gave γ-lactones with better yields than those of the reaction of 2a with 1d, in 49% yield (eq. 2-3). One ethyl group is lost in the reaction.

\[
\begin{align*}
\text{EtO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} + \text{R}^1 & \text{R}^2 \quad \overset{\text{SnCl}_4 (1.0 \text{ equiv.})}{\longleftarrow} \quad \overset{\text{CH}_2\text{Cl}_2}{\text{rt, 16-18 h}} \\
\text{EtO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} & \text{EtO}_2\text{C} & \overset{\text{CO}_2\text{Et}}{\longleftarrow} \\
\text{R}^1 & \text{R}^2 & \text{R}^1 & \text{R}^2 \\
\text{1d: R}^1 = \text{Me}, & \text{R}^2 = (\text{CH}_2)_4\text{CH}_3 \\
\end{align*}
\]

(2-3)

5a: R\(^1\) = Me, R\(^2\) = (CH\(_2\)_4CH\(_3\)) (49%)

The examination of other electrophiles that can be activated by Lewis acids to form indenes is of synthetic and mechanistic interest. The author examined the Lewis acid-promoted reactions of 1,1-diarylallenenes with ketone derivertives, such as vinyl ketones 6 (for 1,4-addition) and diethyl oxomalonate (8) (for 1,2-addition).

As previously described, the SnCl₄-promoted reaction of 1,1-diphenyllallene (1a) with diethyl benzyldenmalonate as a Michael acceptor failed to proceed through a conjugate
addition/cyclization. Highly reactive electrophiles may be required. Therefore, the reaction of simple reactive vinyl ketones was examined. Because SnCl₄ has been shown to be an effective catalyst for indene formation through the reaction of ethenetricarboxylate derivative 2 with arylallenes,⁶ the SnCl₄-promoted reaction was examined at first. The reaction of 1,1-diarylallenes 1a-b with vinyl ketones 6 in the presence of SnCl₄ in dichloromethane or chloroform at room temperature gave the corresponding indene derivatives 7 (Table 2-1).

Both reactants 1 and 6 are unstable in the presence of the Lewis acid. Optimum yields of indenes 7 were obtained under the reaction conditions shown in Table 2-1.⁷

Table 2-1. Reactions of 1,1-diarylallnes 1a-b with vinyl ketones 6a-b

<table>
<thead>
<tr>
<th>Entry</th>
<th>Allene</th>
<th>Ketone</th>
<th>Solvent</th>
<th>Time</th>
<th>Yield (%)⁷</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>6a</td>
<td>CHCl₃</td>
<td>5 min</td>
<td>7a 54</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>6b</td>
<td>CHCl₃</td>
<td>5 min</td>
<td>7b 58</td>
</tr>
<tr>
<td>3</td>
<td>1b</td>
<td>6a</td>
<td>CH₂Cl₂</td>
<td>Overnight</td>
<td>7c 58</td>
</tr>
<tr>
<td>4</td>
<td>1b</td>
<td>6b</td>
<td>CHCl₃</td>
<td>1 h</td>
<td>7d 50</td>
</tr>
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</table>

a Reactions were carried out with 1 (1.0 mmol), 6 (2.0 mmol), and SnCl₄ (1.0 mmol) in the appropriate solvent (4-8 mL). b To monitor the progress of the reaction, this experiment was carried out in an NMR tube. c Isolated yield.
For example, the reaction of allene 1a in the presence of two equivalents of vinyl ketone 6a and one equivalent of SnCl₄ in chloroform for five minutes gave the indene derivative 7a in 54% yield (Table 2-1, entry 1). The reaction of allene 1a with ketone 6a in the presence of ZnI₂ or AlCl₃ resulted in decomposition of the substrates and did not give the indene product. SnCl₄ may have suitable Lewis acidity for this indene formation, as in the case of ethenetricarboxylate derivative.⁶

Next, the 1,2-addition reactions of activated carbonyl compounds with diarylallenes was examined. The reaction of 1,1-diphenylallene (1a) with diethyl oxomalonate (8) in the presence of one equivalent of SnCl₄ in dichloromethane at -40 °C gave the hydroxy(indenyl)malonate 9a in 56% yield (eq. 2-4). The reaction of 1,1-bis(4-chlorophenyl)allene (1b) with oxomalonate 8 at various temperatures gave complex mixtures, possibly including indene derivatives. The products could not be isolated or purified.

When the reaction of 1a with 8 was carried out in the presence of 0.2 equivalent of SnCl₄ at 80 °C in 1,2-dichloroethane, the indenylmalonate 10a was obtained as the major product in 66% yield (eq. 2-5). At room temperature, this reaction gave a complex mixture of products including hydroxy(indenyl)malonate 9a and indenylmalonate 10a. ZnI₂ was also an effective catalyst for indene formation.

The reaction of 1,1-di(4-tolyl)allene (1c) with oxomalonate 8 in the presence of 1.0 or 0.2 equivalent of SnCl₄ at room temperature gave indenylmalonate 10b as the major product (eq. 2-5).
The reaction of allene 1c with oxomalonate 8 in the presence of 0.2 equivalent of ZnI$_2$ at room temperature gave hydroxy(indenyl)malonate 9b as the major product in 32% yield (eq. 2-4).

$$
\text{Z} \quad \text{O} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et}
$$

1a: Z = H  
1c: Z = Me

8

$$
\text{Z} \quad \text{O} \\
\text{EtO}_2\text{C} \quad \text{CO}_2\text{Et}
$$

9a: Z = H, SnCl$_4$ (1 equiv.)  
-40 °C/CH$_2$Cl$_2$, 56%  
9b: Z = Me, ZnI$_2$ (0.2 equiv.)  
r.t./CH$_2$Cl$_2$, 32%

On heating at 80 °C in the presence of SnCl$_4$, 9a was transformed into 10a in 52% yield (eq. 2-6). The mechanism for the reduction of 9a to 10a is unclear. It might involve a Lewis-acid catalyzed process, possibly related to the reported results for disproportionation of allylic alcohols, although 10a was the only isolated and identified product. The stable enolate of the malonate generated in situ may also facilitate the reaction.
Scheme 2-2. Reactions of other carbonyl compounds

The reaction of 1a with other carbonyl compounds such as ethyl glyoxylate, benzaldehyde, acetyl chloride, acetic anhydride, trimethyl phosphonoacrylate, dimethyl (dicyanomethylene)malonate,\textsuperscript{9} methyl acrylate, or cyclohex-2-en-1-one, under similar conditions gave complex mixtures or the unreacted starting materials (Scheme 2-2).
Scheme 2-3. Proposed mechanism and B3LYP/LANL2DZ calculated energies for the reaction of 1,1-diphenylallene (1a) with but-3-en-2-one (6a) in the presence of SnCl₄ (see Table 2-1): ΔE = sum of electronic and zero-point energies (kcal/mol)⁠¹⁰

Scheme 2-4. Proposed mechanism and B3LYP/LANL2DZ calculated energies for the reaction of 1,1-diphenylallene (1a) with dimethyl oxomalonate (8m) in the presence of SnCl₄ (for eq. 2-4)⁠¹⁰
The mechanism for indene formation from a vinyl ketone (Table 2-1) may be similar to the reaction with ethenetricarboxylate derivative (eq. 2-1).\(^6\) Initially, SnCl\(_4\) might coordinate to the carbonyl group of vinyl ketone, and the coordination increases the electrophilicity of C\(_\beta\) of vinyl ketone (Scheme 2-3). Conjugate addition of the allene at the C2 position to the SnCl\(_4\) coordinated vinyl ketone gives a stabilized phenyl allylic cation intermediate V\(_2\). Friedel-Crafts cyclization from phenyl allylic cation intermediate V\(_2\) leads to the indene skeleton V\(_3\). The transformation might also be considered as 4π-electrocyclization of a dienyl carion V\(_2\).\(^{11}\) The proton abstraction in V\(_3\) leads to intermediate V\(_4\), and subsequent transfer of hydrogen chloride gives intermediate V\(_5\). Protonation gives the product complex V\(_6\).\(^6\)

Next, the mechanism for indene formation with an oxomalonate is shown in Scheme 2-4. The SnCl\(_4\) coordinated to oxomalonate through the ketone group and one ester group. The coordination increases the electrophilicity of the ketone carbonyl carbon of oxomalonate. Carbonyl addition at the C2 position of allene from the SnCl\(_4\) coordinated oxomalonate gives a phenyl allylic cation intermediate K\(_2\). Cyclization gives the indene skeleton K\(_3\). Proton abstraction then gives intermediate K\(_3\) and subsequent transfer of hydrogen chloride gives the intermediate K\(_5\). Protonation leads to the product complex K\(_6\).

To clarify the mechanisms for indene formation, the density functional theory calculations were carried out for the addition-cyclization reactions of the model compounds but-3-en-2-one (6a)
(Scheme 2-3), and dimethyl oxomalonate (8m) (Scheme 2-4).\textsuperscript{10} The structure of each intermediate and transition state (TS) was optimized by B3LYP/LANL2DZ.

![Figure 2-1](image)

**Figure 2-1.** B3LYP/LANL2DZ-optimized structures of TSV2 and TSK2 and their reaction-coordinate vectors corresponding to the sole imaginary frequency.\textsuperscript{10}

The cyclization of the phenyl allylic cation intermediates may be considered as a 4π-electrocyclization.\textsuperscript{8b,11} Vibrational analysis of the transition states for the cyclization steps (TSV2 and TSK2) shows that a conrotatory motion, consistent with 4π-electrocyclization, occurs (Figure 2-1).
2-3 Conclusion

In summary, Lewis acid-catalyzed reactions of 1,1-diarylallenines with \( \alpha,\beta \)-unsaturated carbonyl compounds were examined. The Lewis acid-promoted reaction of 1,1-diarylallenines with ethynetricarboxylates 2 and vinyl ketones 6 gave indene derivatives 3 and 7 through a conjugate addition/cyclization reaction. The cyclization may be considered as a 4\( \pi \)-electrocyclization. The reaction of alkylallene 1d with ethynetricarboxylates 2 gave \( \gamma \)-lactone 5a. The reaction of 1,1-diphenylallene (1a) with diethyl oxomalonate (8) in the presence of one equivalent of SnCl\(_4\) at -40 \( ^\circ \)C gave hydroxy(indenyl)malonate 9a as the major product through a carbonyl addition/cyclization reaction. The reaction of 1a with 8 in the presence of SnCl\(_4\) at 80 \( ^\circ \)C gave indenylmalonate 10a.

2-4 Experimental Section

General Procedures

IR spectra were recorded in the FT-mode on a JASCO FT/IR-460 Plus spectrophotometer. \(^1\)H NMR spectra were recorded at 400 MHz and \(^{13}\)C NMR spectra were recorded at 100.6 MHz on a Varian INOVA-400 spectrometer. \(^1\)H chemical shifts are reported in ppm relative to Me\(_4\)Si and \(^{13}\)C chemical shifts are reported in ppm relative to CDCl\(_3\) (77.1 ppm). \(^{13}\)C multiplicities were determined
by DEPT and HSQC experiments. Mass spectra were recorded by EI or FAB techniques on a JEOL JMS-700 mass spectrometer. All reactions were carried out under N₂.

**Allenenes 1a-c** were prepared according to the literature.¹²

3d: R$_{f}$ = 0.3 (hexane-ether = 2 : 1); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.02 (t, J = 7.1 Hz, 3H), 1.28 (d, J = 7.1 Hz, 3H), 3.64 (d, J = 22.7 Hz, 1H), 3.72 (d, J = 22.7 Hz, 1H), 3.91 (d, J = 10.6 Hz, 1H), 3.96 (dq, J = 10.8, 7.1 Hz, 1H), 4.08 (dq, J = 10.8, 7.1 Hz, 1H), 4.21-4.33 (m, 2H), 4.63 (d, J = 10.6 Hz, 1H), 7.18-7.23 (m, 1H), 7.25-7.31 (m, 2H), 7.37-7.40 (m, 2H), 7.43-7.48 (m, 1H), 7.51-7.55 (m, 3H). Selected NOEs are between δ 4.63 (CH) and δ 3.91 (CH(CO$_2$Et)$_2$), 7.37-7.40 (Ph) and between δ 3.64, 3.72 (indene C(1)H$_2$) and δ 3.91 (CH(CO$_2$Et)$_2$), 7.51-7.55 (Ar).; $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.8 (q), 14.0 (q), 30.6 (d), 38.2 (t), 54.2 (d), 62.4 (t), 62.7 (t), 118.2 (s), 121.1 (d), 124.0 (d), 126.2 (d), 126.8 (d), 128.5 (d), 128.8 (d), 129.2 (d), 131.5 (s), 133.1 (s), 142.2 (s), 144.4 (s), 145.7 (s), 165.3 (s), 165.9 (s). Selected HMBC correlations are between δ 4.63 (CH) and δ 131.5 (indene C(2)), 145.7 (indene C(3)), 38.2 (indene C(1)H$_2$), between δ 3.91 (CH(CO$_2$Et)$_2$) and δ 131.5 (indene C(2)), and between δ 3.64, 3.72 (indene C(1)H$_2$) and δ 131.5 (indene C(2)), 145.7 (indene C(3)); IR (neat) 2983, 2244, 1758-1732, 1491, 1463, 1444, 1391, 1370, 1300, 1258, 1192, 1096, 1030 cm⁻¹; MS (EI) m/z 389 (M⁺, 100), 343 (13), 315 (24), 286 (29), 270 (43%); HRMS M⁺ 389.1624 (calcd for C$_{24}$H$_{23}$NO$_3$ 389.1627).
5a: $R_f = 0.4$ (hexane-ether = 1 : 1); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 0.859 (t, $J = 7.0$ Hz, 3H), 0.98-1.08 (m, 1H), 1.19-1.32 (m, 5H), 1.275 (t, $J = 7.1$ Hz, 3H), 1.277 (t, $J = 7.1$ Hz, 3H), 1.44 (s, 3H), 1.61-1.68 (m, 1H), 1.83-1.90 (m, 1H), 2.00 (s, 3H), 4.20-4.26 (m, 4H), 4.62 (s, 1H).

Selected NOEs are between $\delta$ 1.44 (CH$_3$) and $\delta$ 2.00 (CH$_3$).; $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 12.4 (q), 14.02 (q), 14.08 (q), 14.11 (q), 22.46 (t), 22.48 (t), 23.8 (q), 31.7 (t), 37.0 (t), 47.8 (d), 62.2 (t), 88.9 (s), 120.0 (s), 166.80 (s), 166.82 (s), 169.1 (s), 172.0 (s). Selected HMBC correlations are between $\delta$ 1.44 (CH$_3$) and $\delta$ 169.1 (C=CCH$_3$), 88.9 (OCCH$_3$) and between $\delta$ 2.00 (CH$_3$) and $\delta$ 169.1 (C=CCH$_3$), 88.9 (OCCH$_3$), 120.0 (C=CCH$_3$); IR (neat) 2938, 2865, 1752, 1464, 1369, 1305, 1256, 1154, 1036 cm$^{-1}$; MS (El) $m/z$ 341 ((M+H)$^+$, 35), 340 (M$^+$, 3.4), 297 (100%); HRMS M$^+$ 340.1890 (calcd for C$_{18}$H$_{28}$O$_6$ 340.1886).

4-(3-Phenyl-1H-indene-2-yl)butan-2-one (7a): Typical Procedure

SnCl$_4$ (261mg, 120μl, 1mmol) was added to a soln of vinyl ketone 6a (140mg, 162μl, 2mmol) and allene 1a (192mg, 1mmol) in CHCl$_3$ (4mL), and the mixture was stirred at r.t. for 5 min. The reaction was quenched by successive addition of H$_2$O (4mL) and sat. aq. NaHCO$_3$ (40mL). The mixture was extracted with CH$_2$Cl$_2$ (3 × 60mL) and the organic phase was dried (Na$_2$SO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, CH$_2$Cl$_2$) to give 7a (142 mg, 54%); $R_f = 0.7$ (CH$_2$Cl$_2$); pale-yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 2.10 (s, 3H), 2.65
(t-like, $J = 7.6$ Hz, 2 H), 2.80 (t-like, $J = 7.6$ Hz, 2 H), 3.45 (s, 2 H), 7.15-7.25 (m, 3 H), 7.35-7.38 (m, 3 H), 7.44-7.48 (m, 3 H). Selected NOEs were observed between $\delta$ 3.45 (indene C(1)H$_2$) and $\delta$ 2.65 (CH$_2$CO), 2.80 (CH$_2$CH$_2$CO).; $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 23.15 (t), 29.88 (q), 40.67 (t), 43.71 (t), 119.72 (d), 123.59 (d), 124.43(d), 126.37 (d), 127.36 (d), 128.64 (d), 129.12 (d), 135.23 (s), 139.83 (s), 142.30 (s), 142.83 (s), 146.20 (s), 207.93 (s). Selected HMBC correlations were observed between $\delta$ 2.80 (CH$_2$CH$_2$CO) and $\delta$ 142.83 (indene C(2)), 139.83 (indene C(3)), 40.67 (indene C(1)H$_2$); between $\delta$ 2.65 (CH$_2$CO) and $\delta$ 143.83 (indene C(2)); and between $\delta$ 3.45 (indene C(1)H$_2$) and $\delta$ 142.83 (indene C(2)), 139.83 (indene C(3)).; IR (neat) 2924, 1713, 1659, 1447, 1270, 910, 733 cm$^{-1}$, MS (EI) $m/z$ 262 (M$^+$, 44), 204 (100%); HRMS M$^+$ 262.1358 (caled for C$_{19}$H$_{18}$O: 262.1358).

Compounds 7b-d were similarly prepared.

**1-(3-Phenyl-1H-inden-2-yl)pentan-3-one (7b)**

$R_f = 0.7$ (CH$_2$Cl$_2$); pale-yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.03 (t, $J = 7.3$ Hz, 3 H), 2.39 (q, $J = 7.3$ Hz, 2 H), 2.61–2.65 (m, 2 H), 2.79–2.83 (m, 2 H), 3.44 (s, 2 H), 7.15–7.25 (m, 3 H), 7.34–7.38 (m, 3 H), 7.43–7.48 (m, 3 H). Selected NOEs were observed between $\delta$ 3.44 (indene C(1)H$_2$) and $\delta$ 2.61–2.65 (CH$_2$CO), 2.79–2.83 (CH$_2$CH$_2$CO).; $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 7.86 (q), 23.21 (t), 35.91 (t), 40.71 (t), 42.37 (t), 119.70 (d), 123.59 (d), 124.40 (d), 126.36 (d), 127.34
Selected HMBC correlations were observed between δ 2.79–2.83 (CH₂CH₂CO) and δ 143.08 (indene C(2)), 139.73 (indene C(3)), 40.71 (indene C(1)H₂); between δ 2.61–2.65 (CH₂CO) and δ 143.08 (indene C(2)); and between δ 3.44 (indene C(1)H₂) and δ 143.08 (indene C(2)), 139.73 (indene C(3)).

IR (neat) 2975, 2936, 1713, 1659, 1460, 1446, 1270, 1112 cm⁻¹; MS (EI) m/z 276 (M⁺, 79), 204 (100%); HRMS M⁺ 276.1512 (calcd for C₂₀H₂₀O: 276.1514).

4-[6-Chloro-3-(4-chlorophenyl)-1H-inden-2-yl]butan-2-one (7c)

Rᵣ = 0.6 (CH₂Cl₂); pale-yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 2.11 (s, 3 H), 2.62–2.66 (m, 2 H), 2.73–2.77 (m, 2 H), 3.41 (s, 2 H), 7.02 (d, J = 8.1 Hz, 1 H), 7.19 (dd, J = 8.1, 1.9 Hz, 1 H), 7.27 (d-like, J = 8.5 Hz, 2 H), 7.39 (br d, J = 1.5 Hz, 1 H), 7.43 (d-like, J = 8.5 Hz, 2 H). Selected NOEs were observed between δ 3.41 (indene C(1)H₂) and δ 2.62–2.66 (CH₂CO), 2.73–2.77 (CH₂CH₂CO), 7.39 (indene C(7)H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 22.98 (t), 29.89 (q), 40.49 (t), 43.28 (t), 120.19 (d), 124.04 (d), 126.59 (d), 129.01 (d), 130.36 (d), 130.57 (s), 133.18 (s), 133.44 (s), 138.11 (s), 143.82 (s), 143.82 (s), 144.32 (s), 207.41 (s). Selected HMBC correlations were observed between δ 2.73–2.77 (CH₂CH₂CO) and δ 143.82 (indene C(2)), 138.11 (indene C(3)), 40.49 (indene C(1)H₂); between δ 2.62–2.66 (CH₂CO) and δ 143.82 (indene C(2)), and between δ 3.41 (indene C(1)H₂) and δ 143.82 (indene C(2)), 133.18 (indene C(3)).; IR (neat) 2921, 1716, 1591, 1573, 1489, 1361, 1158,
1093, 1015 cm$^{-1}$; MS (EI) $m/z$ 332 (M$^+$, 40), 331 (M$^+$, 13), 330 (M$^+$, 64), 274 (41), 272 (58), 237 (89), 86 (83), 84 (100%); HRMS M$^+$ 330.0577, 331.0605, 332.0563 (calcd for C$_{19}$H$_{16}$Cl$_2$O: 330.0578, 331.0612, 332.0549).

1-[6-Chloro-3-(4-chlorophenyl)-1$H$-inden-2-yl]pentan-3-one (7d)

R$_f$ = 0.6 (CH$_2$Cl$_2$); colorless crystals; mp 69–71 °C (EtOAc–hexane); $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.04 (t, $J$ = 7.3 Hz, 3 H), 2.39 (q, $J$ = 7.3 Hz, 2 H), 2.62 (t-like, $J$ = 7.3 Hz, 2 H), 2.76 (t-like, $J$ = 7.3 Hz, 2 H), 3.42 (s, 2 H), 7.02 (d, $J$ = 8.1 Hz, 1 H), 7.20 (dd, $J$ = 8.1, 2.0 Hz, 1 H), 7.28 (d-like, $J$ = 8.5 Hz, 2 H), 7.40 (br d, $J$ = 1.3 Hz, 1 H), 7.44 (d-like, $J$ = 8.5 Hz, 2 H). Selected NOEs were observed between δ 3.42 (indene C(1)H$_2$) and δ 2.62 (CH$_2$CO), 2.76 (CH$_2$CH$_2$CO), 7.40 (indene C(7)H);$^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 7.86 (q), 23.08 (t), 35.97 (t), 40.56 (t), 41.98 (t), 120.21 (d), 124.07 (d), 126.62 (d), 129.03 (d), 130.39 (d), 130.59 (s), 133.25 (s), 133.45 (s), 138.08 (s), 143.85 (s), 144.06 (s), 144.38 (s), 210.17 (s). Selected HMBC correlations were observed between δ 2.76 (CH$_2$HCO) and δ 138.08 (indene C(3)), 40.56 (indene C(1)H$_2$); and between δ 3.42 (indene C(1)H$_2$) and δ 133.18 (indene C(3)); IR (KBr) 2971, 2937, 2903, 2878, 1710, 1491, 1458, 1376, 1094, 1015, 819 cm$^{-1}$; MS (FAB) $m/z$ 346, 345 (M+H)$^+$; HRMS (FAB): (M+Na)$^+$ found: 367.0631. Anal. Calcd for C$_{20}$H$_{18}$Cl$_2$O: C, 69.57; H, 5.25. Found: C, 69.29; H, 5.11 (calcd for C$_{20}$H$_{18}$Cl$_2$NaO: 367.0632).
\( ^1H \) NMR Monitoring of the Reaction between (1b) and (6b)

In the NMR tube, SnCl\(_4\) (26.1mg, 12.0\( \mu l \), 0.1mmol) was added to a soln of vinyl ketone 6b (16.8mg, 19.9\( \mu l \), 0.2mmol) and allene 1b (26.1mg, 0.1mmol) in CDCl\(_3\) (0.75mL). The monitoring reaction was performed at r.t. every 10 min.

Diethyl Hydroxy(3-phenyl-1H-inden-2-yl)malonate (9a)

SnCl\(_4\) (261 mg, 120 \( \mu L \), 1 mmol) was added to a soln of diethyl oxomalonate (8) (174 mg, 152 \( \mu L \), 1 mmol) and allene 1a (192 mg, 1 mmol) in CH\(_2\)Cl\(_2\) (2 mL) at –40 °C and the mixture was stirred at –40 °C overnight. The reaction was quenched successively with H\(_2\)O (4 mL) and sat. aq NaHCO\(_3\) (40 mL). The mixture was extracted with CH\(_2\)Cl\(_2\) (3 \( \times \)60 mL) and the organic phase was dried (Na\(_2\)SO\(_4\)) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane–ether) to give 9a (205 mg (56%)); R\(_f\) = 0.3 (hexane–ether, 2:1); pale-yellow oil; \( ^1H \) NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 1.19 (t, \( J = 7.1 \) Hz, 6 H), 3.71 (s, 2 H), 3.88 (dq, \( J = 10.8, 7.1 \) Hz, 2 H), 4.04 (dq, \( J = 10.8, 7.1 \) Hz, 2 H), 4.14 (br s, 1 H), 7.06–7.08 (m, 1 H), 7.22–7.26 (m, 2 H), 7.33–7.45 (m, 5 H), 7.47–7.49 (m, 1 H). Selected NOEs were observed between \( \delta 3.71\) (inden C(1)H\(_2\)) and \( \delta 7.47–7.49\) (inden C(7)H).; \( ^{13}C \) NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (ppm) 13.91 (q), 39.67 (t), 62.86 (t), 78.92 (s), 121.07 (d), 123.60 (d), 125.81 (d), 126.48 (d), 127.83 (d), 128.13 (d), 129.44 (d), 134.56 (s), 137.02 (s), 142.12 (s), 143.70 (s), 146.19 (s), 169.77 (s). Selected HMBC correlations were observed
between δ 3.71 (indene C(1)H₂) and δ 78.92 (C(CO₂Et)₂OH), 123.60 (indene C(7)); IR (neat) 3475, 2981, 1738, 1462, 1444, 1392, 1368, 1264, 1206, 1159, 1094, 1037 cm⁻¹; MS (EI) m/z 366 (M⁺, 5), 348 (100%); HRMS M⁺ 366.1461 (calcd for C₂₂H₂₂O₅ 366.1467).

**Diethyl Hydroxy[6-methyl-3-(4-methylphenyl)-1H-inden-2-yl]malonate (9b)**

ZnI₂ (32 mg, 0.1 mmol) was added to a soln of diethyl oxomalonate (8) (87 mg, 76 μL, 0.5 mmol) and allene 1c (110 mg, 0.5 mmol) in CH₂Cl₂ (2 mL), and the mixture was stirred at r.t. overnight. The reaction was quenched by successive addition of H₂O (2 mL) and sat. aq. NaHCO₃ (20 mL). The mixture was extracted with CH₂Cl₂ (3 × 30 mL) and the organic phase was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane-ether) to give 9b (63 mg, 32%); Rᵣ = 0.2 (hexane–ether, 2:1); pale-yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.18 (t, J = 7.1 Hz, 6 H), 2.38 (s, 3 H), 2.39 (s, 3 H), 3.65 (s, 2 H), 3.88 (dq, J = 10.6, 7.1 Hz, 2 H), 4.04 (dq, J = 10.6, 7.1 Hz, 2 H), 4.13 (br s, 1 H), 6.97 (d, J = 7.7 Hz, 1 H), 7.05 (br d, J = 7.7 Hz, 1 H), 7.22 (d, J = 7.9 Hz, 2 H), 7.28 (d, J = 7.9 Hz, 2 H), 7.29 (br s, 1 H). Selected NOEs were observed between δ 3.65 (indene C(1)H₂) and δ 7.29 (indene C(7)H).; ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.89 (q), 21.37 (q), 21.53 (q), 39.36 (t), 62.79 (t), 78.95 (s), 120.73 (d), 124.44 (d), 127.15 (d), 128.75 (d), 129.25 (d), 131.64 (s), 135.58 (s), 135.69 (s), 137.36 (s), 142.38 (s), 143.57 (s), 143.71 (s), 169.89 (s). Selected HMBC correlations were observed between δ 3.65 (indene C(1)H₂) and δ 78.95
(CO₂Et)₂OH), 124.44 (indene C(7)); IR (neat) 3478, 2981, 2923, 1788, 1742, 1509, 1445, 1368, 1268, 1173, 1096, 1037 cm⁻¹; MS (El) m/z 394 (M⁺, 9.4), 376 (65), 321 (90), 303 (47), 247 (100%); HRMS M⁺ 394.1779 (calcd for C₂₄H₂₆O₅: 394.1780).

Diethyl (3-Phenyl-1H-inden-2-yl)malonate (10a)

SnCl₄ (5.2 mg, 2.4 μL, 0.02 mmol) was added to a soln of diethyl oxomalonate (8) (17.4 mg, 0.1 mmol) and allene 1a (19.2 mg, 0.1 mmol) in ClCH₂CH₂Cl (0.4 mL), and the mixture was heated at 80 °C overnight. The reaction mixture was cooled to r.t. and quenched by addition of sat. aq. NaHCO₃ (5 mL). The mixture was extracted with CH₂Cl₂ (3 × 10 mL) and the organic phase was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane-ether) to give 10a (23.1 mg, 66%); Rᵢ = 0.6 (hexane-ether, 2:1); pale-yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.27 (t, J = 7.1 Hz, 6 H), 3.80 (s, 2 H), 4.15–4.27 (m, 4 H), 4.76 (s, 1 H), 7.22–7.27 (m, 3 H), 7.39–7.43 (m, 3 H), 7.47–7.52 (m, 3 H). Selected NOEs were observed between δ 3.80 (indene C(1)H₂) and δ 4.76 (CH(CO₂Et)₂), 7.47–7.52 (indene C(7)H); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 14.14 (q), 39.20 (t), 52.31 (d), 61.84 (t), 120.65 (d), 123.85 (d), 125.47 (d), 126.31 (d), 127.99 (d), 128.80 (d), 129.23 (d), 134.03 (s), 134.09 (s), 143.35 (s), 144.53 (s), 144.94 (s), 168.16 (s). Selected HMBC correlations were observed between δ 3.80 (indene C(1)H₂) and δ 52.31 (CH(CO₂Et)₂), 123.85 (indene C(7)); and between δ 4.76 (CH(CO₂Et)₂) and δ 39.20 (indene C(1)H₂).
IR (neat) 2980, 2929, 1732, 1461, 1444, 1367, 1304, 1148, 1031 cm⁻¹; MS (EI) m/z 350 (M⁺); HRMS M⁺ 350.1518 (calcd for C₂₂H₂₂O₄: 350.1518).

**Diethyl [6-Methyl-3-(4-tolyl)-1H-inden-2-yl]malonate (10b)**

SnCl₄ (130 mg, 60 μL, 0.5 mmol) was added to a soln of diethyl oxomalonate (8) (87 mg, 76 μL, 0.5 mmol) and allene 1c (110 mg, 0.5 mmol) in CH₂Cl₂ (2 mL), and the mixture was stirred at r.t. overnight. The reaction was quenched by successive addition of H₂O (2 mL) and sat. aq. NaHCO₃ (20 mL). The mixture was extracted with CH₂Cl₂ (3 × 30 mL) and the organic phase was dried (Na₂SO₄) and concentrated in vacuo. The residue was purified by column chromatography (silica gel, hexane-ether) to give 10b (69 mg, 36%); Rᵣ = 0.5 (hexane–ether, 2:1); pale-yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.26 (t, J = 7.1 Hz, 6 H), 2.40 (s, 3 H), 2.42 (s, 3 H), 3.74 (s, 2 H), 4.14–4.26 (m, 4 H), 4.75 (s, 1 H), 7.10 (br d, J = 7.8 Hz, 1 H), 7.13 (d, J = 7.8 Hz, 1 H), 7.29 (br s, 4 H), 7.32 (br s, 1 H). Selected NOEs were observed between δ 3.74 (indene C(1)H₂) and δ 7.10 (indene C(7)H₃); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 14.14 (q), 21.41 (q), 21.53 (q), 38.89 (t), 52.31 (d), 61.75 (t), 120.32 (d), 124.73 (d), 126.96 (d), 129.07 (d), 129.47 (d), 131.20 (s), 132.68 (s), 135.22 (s), 137.62 (s), 142.48 (s), 143.65 (s), 144.27 (s), 168.30 (s). Selected HMBC correlations were observed between δ 3.74 (indene C(1)H₂) and δ 124.73 (indene C(7)); and between δ 4.75 (CH(CO₂Et)₂) and δ 38.89 (indene C(1)H₂); IR (KBr) 2981, 1729, 1307, 1225, 1159, 1030 cm⁻¹; MS (EI) m/z 378 (M⁺, 84), 305
(55), 259 (31), 231 (100%); HRMS M⁺ 378.1833 (calcd for C₂₄H₂₆O₄: 378.1831).

2-5 References


7 When a catalytic amount (0.2 equivalent) of SnCl₄ was used in the reaction of 1a with 6a on a 0.1-mmol scale (CH₂Cl₂, 3–20 h), the yields of the indene product 7a were comparable to that shown in Table 2-1 (entry 1); however, the reactions between 1a and 6b and between 1b and 6a were less efficient under these catalytic conditions.


Chapter 3

Lewis Acid-Promoted Cyclization Reactions of Allenyl Ethenetricarboxylates with Amides

3-1 Introduction

Development of new synthetic reactions utilizing allenes has attracted attention due to their structural features. Transition metal-catalyzed cyclization reaction of allenes containing additional multiple bonds such as alkynes, alkenes, arynes, aldehydes, and ketones have been recognized as efficient methods to prepare highly substituted carbocycles and heterocycles. Thermal, photochemical, reductive, and base-promoted cyclization reactions of these allenes have been reported. Lewis acid-promoted carbon-carbon bond-forming cyclizations of allenyl-aldehyde acetals and aryl-allenes have also been studied. Few examples are known for the intramolecular Lewis acid-mediated cyclization of allenes containing electron-deficient alkenes (as Michael acceptors).

Snider and Roush reported that Lewis acid-promoted intramolecular reactions of alkenyl and alkynyl ethenetricarboxylates gave chlorinated γ-lactones. Yamazaki and coworkers have developed Lewis acid-promoted stereoselective cyclization of alkynyl ethenetricarboxylates with high generality and Lewis acid-promoted 3,4-trans stereoselective cyclization of alkenyl ethenetricarboxylates has also been investigated (eq. 3-1).
Yamazaki and coworkers have studied various Lewis acid-promoted intermolecular reactions of ethenetricarboxylate derivatives and reported that they function as highly electrophilic Michael acceptors. The reaction of arylallenes and ethenetricarboxylate with SnCl₄ gave indene derivatives efficiently. In addition, the reactions of 1,1-dialkylallenes and ethenetricarboxylate with SnCl₄ gave γ-lactones.

In this study, Lewis acid-promoted intramolecular reactions containing allenes as an extension of the reaction of alkenyl substrates (eq. 3-1) have been examined.

3-2 Results and Discussion

Allenyl esters 3a-c were prepared by the reaction of 1,1-diethyl 2-hydrogen ethenetricarboxylate 1 (prepared from 1,1-diethyl 2-tert-butyl ethenetricarboxylate upon treatment with CF₃CO₂H) with the corresponding allenyl alcohols 2a-c in the presence of PPh₃ and DEAD (diethyl azodicarboxylate) (eq. 3-2).
The reaction of allenyl ethenetricarboxylates 3a-b with one equivalent of various Lewis acids such as AlCl₃, AlBr₃, SnCl₄, TiCl₄, FeCl₃, InCl₃, and InBr₃ in CH₂Cl₂ at room temperature gave 3,4-trans haloalkenyl tetrahydrofuran derivatives 4a-d stereoselectively (Table 3-1). Among those Lewis acids, AlCl₃ and AlBr₃ gave chlorinated and brominated cyclic products 4a-d most efficiently.

The reaction of 3a with SnCl₄, TiCl₄, and TiBr₄ also gave 4a-b along with 4-ethynyltetrahydrofuran derivative 5 as a by-product via Lewis acid-catalyzed ene-type reaction. Use of FeCl₃, InCl₃, and InBr₃ gave 4a-b and the noncyclized H₂O adduct 6 as a by-product (entries 6-8). Furthermore, the reaction of 3a using ZnBr₂, BF₃·OEt₂, ZrCl₄, and Zn(OTf)₂ at room temperature gave the starting material 3a. The reaction of 3a with ZnBr₂, ZnI₂, Sc(OTf)₃, and Zn(OTf)₂ at 80 °C gave a complex mixture or the starting material 3a.
Table 3-1. Reactions of allenyl esters 3a-b

![Diagram of reaction](image)

<table>
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<th>Entry</th>
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<th>R</th>
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<th>X</th>
<th>Yield (%)</th>
<th>By-product (%)</th>
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<td>4b</td>
<td>Br</td>
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<tr>
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<td>4a</td>
<td>Cl</td>
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<td>5 (ca. 19)&lt;sup&gt;a&lt;/sup&gt;</td>
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<td>4b</td>
<td>Br</td>
<td>46</td>
<td>5 (30)</td>
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<tr>
<td>6</td>
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<td>H</td>
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<td>4a</td>
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<td>Br</td>
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<td>Cl</td>
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<sup>a</sup> Small amounts of impurity could not be removed.  
<sup>b</sup> The yields were estimated by the NMR spectra of the mixture of 4a and 6.  
<sup>c</sup> Inseparable by-products were also produced.

The γ-lactone structure of 4a-d was suggested by the presence of a characteristic C=O absorption (1780-1782 cm<sup>-1</sup>) and disappearance of the 1958-1972 cm<sup>-1</sup> absorption for C=C=C allene.
moiety in 3a-b. $^1$H, $^{13}$C and 2D NMR spectra were in agreement with the five-membered ring structure. The 3,4-stereochemistry of 4a-d was examined by NOESY experiments. NOEs between H-3 and H-4 could be observed for both 3,4-\textit{cis} and \textit{trans} diastereomers. The following peaks were used for the assignment of haloalkenyl 2-oxotetrahydrofurans 4a-d. NOEs between H-3 and CX=CH(X=Cl, Br)$^{14}$ for 4a-b and/or between H-4 and CH(CO$_2$Et)$_2$ for 4a-d were observed. Thus, the 3,4-\textit{trans} stereochemistry of 4a-d was likely, similar to cyclic products in eq. 3-1. On the other hand, NOESY spectra of by-product 4-ethynyltetrahydrofuran 5 did not give enough information for the 3,4-stereochemistry.

In order to support the assignment of the stereochemistry of 4a and determine the stereochemistry of the by-product 4-ethynyltetrahydrofuran 5, the following transformations have been carried out. Hydrogenolysis of the 4-chlorovinyl substituted tetrahydrofuran 4a gave 3,4-\textit{trans}-4-ethyltetrahydro-2-oxofuran 7 in 51% yield (Scheme 3-1). Hydrogenolysis of both carbon-chlorine bond and carbon-carbon double bond occurred.$^{15}$ 3,4-\textit{Trans}-4-(1-chloroethyl)-2-oxotetrahydrofuran 8 was obtained by the Lewis acid-promoted reaction of alkenyl ester 9 stereoselectively.$^{16}$ Under the same hydrogenolysis condition, dechlorination of compound 8 did not undergo hydrolysis. The reaction of 8 with Bu$_3$SnH and AIBN gave dechlorinated tetrahydrofuran 7 in 89% yield. The products (7) obtained from 4a and 8 were identical. Thus, the stereochemistry of 7 was assigned as 3,4-\textit{trans}. The stereochemistry of 7 was also
determined by NOESY experiment. Next, hydrogenolysis of ethynyl group of 5 was conducted. The hydrogenated product 7-cis was different from 7 and could be assigned as 3,4-cis-4-ethyltetrahydro-2-oxofuran.

![Scheme 3-1. Reduction of 4a, 8, and 5](image)

The Lewis acid-promoted reaction of 2-penta-3,4-dienyl ester 3c (shown in eq. 3-2) was also examined. However, the reaction of 3c with one equivalent of AlCl₃, AlBr₃, and SnCl₄ gave complex mixtures. Six-membered ring formation was not an efficient process.
Next, allenyl amide substrates 11a-b were prepared by the condensation reaction of 1,1-diethyl 2-hydrogen ethenetricaboxylate 1 with the corresponding allenyl amines 10a-b in the presence of HOBT, EDCI, and Et$_3$N (eq. 3-3). Reaction of diethyl 2-((N-allenyl-N-benzylcarbamoyl)methylene)malonate (11a) with AlCl$_3$, ZnCl$_2$, ZnBr$_2$, and ZnI$_2$ at room temperature gave diethyl 3,4-trans-4-(1-chloro(or bromo/iodo)vinyl)-2-oxopyrrolidines 12a-c in 55-76% yields (Table 3-2). Reaction of N-allenyl-N-propylcarbamoyl derivative 11b also gave 3,4-trans pyrrolidines 12d-f in 64-68% yields. Reaction of 11a-b with AlBr$_3$ also gave 12b, 12e but with lower yields than those of ZnBr$_2$ (16% for 12b, ca. 50% (including a small amount of inseparable impurity) for 12e). The γ-lactam structures of 12a-f were suggested by the presence of a characteristic C=O absorption (1688-1698 cm$^{-1}$). $^1$H, $^{13}$C, and 2D NMR spectra were in agreement with the 5-membered ring structure. The 3,4-trans stereochemistry was determined by NOEs. NOEs between H-3 and CX=HH (X = Cl, Br, I) and between H-4 and CH(CO$_2$Et)$_2$ were observed.
Table 3-2. Reactions of allenyl amides 11

![Diagram of reactions]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>MXₙ (equiv.)</th>
<th>X</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Ph</td>
<td>AlCl₃</td>
<td>1</td>
<td>Cl</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Ph</td>
<td>ZnCl₂</td>
<td>1 × 2</td>
<td>Cl</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Ph</td>
<td>ZnBr₂</td>
<td>1 × 2</td>
<td>Br</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Ph</td>
<td>ZnI₂</td>
<td>2</td>
<td>I</td>
</tr>
<tr>
<td>5</td>
<td>CH₂CH₂CH₃</td>
<td>AlCl₃</td>
<td>1</td>
<td>Cl</td>
</tr>
<tr>
<td>6</td>
<td>CH₂CH₂CH₃</td>
<td>ZnBr₂</td>
<td>1 × 2</td>
<td>Br</td>
</tr>
<tr>
<td>7</td>
<td>CH₂CH₂CH₃</td>
<td>ZnI₂</td>
<td>1 × 2</td>
<td>I</td>
</tr>
</tbody>
</table>

a The reaction with ZnX₂ (1 equivalent) for 18 h gave the crude products including impurities (possibly non-cyclized water-adducts) after work-up. The crude products were further treated with ZnX₂ (1 equivalent) to give the products 12.

In order to demonstrate the utility of the cyclization reaction, transformation of the products was performed. Oxidative cleavage of the double bond of tetrahydrofuran 4a by NaIO₄-RuCl₃·xH₂O and a neutral work-up gave acid 13 in 98% yield (Scheme 3-2). Subsequent treatment of 13 with Me₃SiCHN₂ in methanol/benzene led to methyl ester 14 in 71% yield. The stereochemistry of 13 and 14 was determined as 3,4-trans by NOESY experiments. Derivatization of 13 with benzyl amides gave functionalized 3-oxotetrahydrofurans 15a-b.
Furthermore, Suzuki-coupling reaction of halogenovinyl heterocycles was performed. The reaction of iodovinyl pyrrolidines 12c, 12f with phenylboronic acid proceeded smoothly to give phenyl-substituted pyrrolidine (16a-b) (eq. 3-4).

The reaction mechanism to give the halogenated five-membered heterocycles with 3,4-trans stereochemistry is proposed similar by to that for the reaction of the allyl ester of ethenetetracarboxylates (eq. 3-1)\textsuperscript{11} and shown in Scheme 3-3. \textit{Trans} precursor A1 in Scheme 3-3 and \textit{cis} precursor A2 in
Scheme 3-4 may be formed from 3 and Al$_2$Cl$_6$ reversibly. The reaction may start from the precursor A1 consisting of 3 and Al$_2$Cl$_6$. The C-C bond formation and Cl-C bond formation from A1 may occurconcertedly to lead to cyclized intermediate B1. Intermolecular Cl\textsuperscript{-}anti attack leading to 3,4-trans cyclized product is proposed by steric reason. One molecule of Lewis acid (for example, AlCl$_3$) may work as a catalyst and could be released after the cyclization step. Protonation and removal of AlCl$_2$OH yield the product 4.

In order to support this hypothesis, the structures of the intermediates and transition states of model compounds (the corresponding methyl esters and Al$_2$Cl$_6$) were calculated using B3LYP/6-31G*. $\Delta G^\ddagger$ for TS1 leading to 3,4-trans tetrahydrofuran is found to be lower than that of TS2 leading to 3,4-cis tetrahydrofuran (Scheme 3-4). These calculation results are similar to that for allyl ester + Al$_2$Cl$_6$. Thus, formation of 3,4-trans five-membered rings is lower energy process than that of 3,4-cis. The calculation results support the assignment of 3,4-trans stereochemistry for the products 4.

Calculations of 1:1 complex of the substrate and AlCl$_3$ were also examined. Although the concerted formations of both 3,4-cis and trans tetrahydrofuran rings by intramolecular Cl\textsuperscript{-}attack were calculated, they have higher activation energies ($\Delta G^\ddagger$) than the systems of the substrate and Al$_2$Cl$_6$. In addition, the AlCl$_3$-promoted process to form 3,4-cis-4-ethynyltetrahydrofuran 5 was obtained. The activation energy ($\Delta G^\ddagger$) for formation of 5 with AlCl$_3$ is also higher than the systems of the substrate and Al$_2$Cl$_6$. 

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Scheme 3-3. Proposed reaction mechanism for cyclization of allyl esters 3a (R = Et) and model compound 3m (R = Me) with Al$_2$Cl$_6$ and the B3LYP/6-31G* calculated Gibbs free energies ($T$ = 298.15 K and $P$ = 1 atm) for intermediates and TSs (transition states) of the model compounds (3m + Al$_2$Cl$_6$).
Scheme 3-4. The reaction pathway leading to 3,4-cis intermediate B2 for model compounds (3m + Al2Cl6). B3LYP/6-31G*-optimized structures of the model compounds are shown. The Gibbs free energies are relative to A1 (R = Me) in Scheme 3-3.

Concerning the reactivity of the oxygen and nitrogen substrates, relatively weak Lewis acids such as zinc halides promote the cyclization of the amide substrates 11a-b. The facile cyclization of amides compared to esters can be explained as follows. The conformations of model compounds of allenyl ester 3 and amide substrate 11 were calculated and compared. The s-cis and s-trans conformations about the 2-ester or amide carbonyl moiety are shown in Figure 3-1. Ester 3 is 8.98
kcal/mol more stable in s-cis conformation, probably because of the steric repulsion. On the other hand, the energy difference between s-cis and s-trans conformations of amide 11 concerning allenyl group is small. In order to cyclize, they must have s-trans conformations. The structural features of esters and amides may lead to the different reactivities.

Figure 3-1. The model compounds, dimethyl esters with allenyl group 3m and 11m optimized by B3LYP/6-31G* and their relative energies △G°. △G° is the difference of Gibbs free energies (T = 298.15 K, P = 1 atom) relative to that of s-cis conformations.
3-3 Conclusion

In summary, a Lewis acid-promoted reaction of allenyl ethenetricarboxylates 3a,b and the amides 11a,b to give haloalkenyl oxygen and nitrogen-containing 5-membered heterocycles has been found. The reaction gave 3,4-trans substituted cyclized products stereoselectively. Aluminum chloride and bromide gave 2-oxotetrahydrofurans, and AlCl₃, ZnX₂ (X = Cl, Br, I) gave 2-oxopyrrolidines efficiently. The haloalkenyl five-membered heterocycles generated in this reaction should be versatile synthetic intermediates. Some transformations of the products utilizing the haloalkenyl functionality have also been demonstrated. Further elaboration of the products and studies on various alkyl substitution patterns of allenyl groups including chiral substrates are under investigation.

3-4 Experimental Section

General Procedures

IR spectra were recorded in the FT-mode on a JASCO FT/IR-460 Plus spectrophotometer. ¹H NMR spectra were recorded at 400 MHz and ¹³C NMR spectra were recorded at 100.6 MHz on a Varian INOVA-400 spectrometer. ¹H chemical shifts are reported in ppm relative to Me₄Si and ¹³C chemical shifts are reported in ppm relative to CDCl₃ (77.1 ppm). ¹³C multiplicities were determined by DEPT and HSQC experiments. Peak assignments are made by 2D COSY, HSQC, NOESY, and HMBC spectra. Mass spectra were recorded by EI or FAB or CI techniques on a JEOL JMS-700 mass...
Allenyl alcohols 2a,b,c were prepared according to the literature.\textsuperscript{5a,17,18}

1,1-Diethyl 2-Buta-2,3-dienyl Ethene-1,1,2-tricarboxylate (3a): Typical Procedure

To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (432 mg, 2 mmol) (prepared from 1,1-diethyl 2-\textit{tert}-butyl ethenetricarboxylate (545 mg, 2 mmol) upon treatment with CF\textsubscript{3}CO\textsubscript{2}H) in ether (2 mL) were added diethyl azodicarboxylate 40\% in toluene (0.91 mL, 2 mmol), PPh\textsubscript{3} (525 mg, 2 mmol) and 2a (210 mg, 3 mmol) at room temperature. The reaction mixture was stirred overnight. After removal of the solvent under reduced pressure, the residue was purified by column chromatography over silica gel with hexane–ether as eluent to give 3a (333 mg, 62\%); R\textsubscript{f} = 0.8 (ether); pale yellow oil; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 1.32 (t, \(J = 7.1\) Hz, 3H), 1.35 (t, \(J = 7.1\) Hz, 3H), 4.30 (q, \(J = 7.1\) Hz, 2H), 4.37 (q, \(J = 7.1\) Hz, 2H), 4.69 (dt, \(J = 7.1, 2.3\) Hz, 2H), 4.88 (dt, \(J = 6.6, 2.3\) Hz, 2H), 5.30 (tt, \(J = 7.1, 6.6\) Hz, 1H), 6.88 (s, 1H); \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}) \(\delta\) (ppm) 13.91 (q), 13.96 (q), 62.13 (t), 62.54 (t), 63.48 (t), 76.96 (t), 85.57 (d), 129.63 (d), 139.29 (s), 162.21 (s), 163.27 (s), 164.18 (s), 210.08 (s); IR (neat) 2984, 1958, 1728, 1652, 1259, 1178, 1067 cm\textsuperscript{-1}; MS (EI) \textit{m/z} 269 (M\textsuperscript{+}, 29), 200 (90), 199 (93), 171 (95), 143 (100\%); HRMS M\textsuperscript{+} 268.0945 (calcd for C\textsubscript{13}H\textsubscript{16}O\textsubscript{6} 268.0947); Anal. Calcd for C\textsubscript{13}H\textsubscript{16}O\textsubscript{6}: C, 58.20; H, 6.01. Found: C, 58.05; H, 5.81.
3b: R_f = 0.8 (ether); pale yellow oil; ^1H NMR (400 MHz, CDCl3) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.70 (d, J = 2.9 Hz, 6H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.62 (d, J = 7.0 Hz, 2H), 5.11 (m, 1H), 6.89 (s, 1H); ^13C NMR (100.6 MHz, CDCl3) δ (ppm) 13.98 (q), 14.01 (q), 20.19 (q), 62.13 (t), 62.54 (t), 64.73 (t), 83.99 (d), 97.73 (s), 129.98 (d), 139.10 (s), 162.33 (s), 163.36 (s), 164.30 (s), 203.87 (s); IR (neat) 2984, 1972, 1728, 1651, 1446, 1375, 1259, 1177, 1067 cm⁻¹; MS (EI) m/z 297 ((M+H)^+, 16), 296 (M^+, 5.6), 269 (24), 251 (100%); HRMS M^+ 296.1260 (calcd for C_{15}H_{20}O_{6} 296.1260); Anal. Calcd for C_{15}H_{20}O_{6}: C, 60.80; H, 6.80. Found: C, 60.88; H, 6.98.

3c: R_f = 0.6 (hexane-ether = 1 : 1); pale yellow oil; ^1H NMR (400 MHz, CDCl3) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.37 (tdt, J = 6.8, 6.8, 3.1 Hz, 2H), 4.26 (t, J = 6.8 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.73 (dt, J = 6.8, 3.1 Hz, 2H), 5.10 (tt, J = 6.8, 6.8 Hz, 1H), 6.87 (s, 1H); ^13C NMR (100.6 MHz, CDCl3) δ (ppm) 13.98 (q), 14.02 (q), 27.44 (t), 62.16 (t), 62.57 (t), 64.81 (t), 75.84 (t), 85.55 (d), 129.86 (d), 139.19 (s), 162.34 (s), 163.58 (s), 164.27 (s), 209.10 (s); IR (neat) 2984, 1957, 1728, 1345, 1261, 1180, 1066, 1023 cm⁻¹; MS (EI) m/z 282 (M^+, 3.2), 236 (24), 208 (45), 171 (90), 143 (100%); HRMS M^+ 282.1102 (calcd for C_{14}H_{18}O_{6} 282.1103); Anal. Calcd for C_{14}H_{18}O_{6}: C, 59.57; H, 6.43. Found: C, 59.59; H, 6.55.
Diethyl 2-[Trans-4-(1-chlorovinyl)-2-oxotetrahydrofuran-3-yl]malonate (4a): Typical Experimental Procedure (Table 3-1, entry 1)

To a solution of 3a (148 mg, 0.55 mmol) in CH$_2$Cl$_2$ (2.2 mL) was added AlCl$_3$ (73 mg, 0.55 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was poured into saturated aqueous NaHCO$_3$ solution. The mixture was extracted with dichloromethane and the organic phase was dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was filtered through Florisil eluting with dichloromethane to give 4a (126 mg, 75%); R$_f$ = 0.7 (ether); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.29 (t, $J$ = 7.1 Hz, 3H), 1.30 (t, $J$ = 7.1 Hz, 3H), 3.43 (dd, $J$ = 9.9, 4.8 Hz, 1H), 3.97 (ddd, $J$ = 9.9, 8.8, 8.8 Hz, 1H), 4.00 (d, $J$ = 4.8 Hz, 1H), 4.13-4.28 (m, 5H), 4.52 (dd, $J$ = 8.9, 8.9 Hz, 1H), 5.32 (dd, $J$ = 1.6, 0.4 Hz, 1H), 5.38 (d, $J$ = 1.6 Hz, 1H). Selected NOEs are between $\delta$ 3.43 (H-3) and 5.38 (=CH$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 13.93 (q), 13.97 (q), 41.85 (d), 46.09 (d), 49.68 (d), 62.06 (t), 62.17 (t), 68.74 (t), 117.20 (t), 138.72 (s), 167.12 (s), 167.45 (s), 175.17 (s). Selected HMBC correlations are between $\delta$ 3.97 (H-4) and $\delta$ 41.85 (C-3), 68.74 (C-5), between $\delta$ 3.43 (H-3) and $\delta$ 46.09 (C-4), 138.72 (CCl=), $\delta$ 4.52 (H-5b) and $\delta$ 41.85 (C-3), 138.72 (CCl=), and between $\delta$ 5.32, 5.38 (=CH$_2$) and $\delta$ 46.09 (C-4), 138.72 (CCl=); IR (neat) 2984, 1781, 1734, 1633, 1476, 1373, 1264, 1240, 1181, 1032 cm$^{-1}$; MS (FAB) m/z 307, 305 (M+H)$^+$; HRMS (M+H)$^+$ 305.0795 (calcd for C$_{13}$H$_{18}$ClO$_6$ 305.0792).
Diethyl 2-[Trans-4-(1-bromovinyl)-2-oxotetrahydrofuran-3-yl]malonate (4b): \( R_f = 0.5 \) (hexane-ether = 1 : 1); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 1.29 (t, \( J = 7.1 \) Hz, 3H), 1.30 (t, \( J = 7.1 \) Hz, 3H), 3.40 (dd, \( J = 9.8, 4.7 \) Hz, 1H), 3.87 (ddd, \( J = 9.8, 8.8, 8.8 \) Hz, 1H), 4.00 (d, \( J = 4.7 \) Hz, 1H), 4.11-4.28 (m, 5H), 4.49 (dd, \( J = 9.0, 9.0 \) Hz, 1H), 5.57 (d, \( J = 2.0 \) Hz, 1H), 5.82 (dd, \( J = 2.0, 0.4 \) Hz, 1H). Selected NOEs are between \( \delta \) 3.40 (H-3) and 5.82 (=C\( \text{H} \)).; \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (ppm) 14.00 (q), 42.87 (d), 47.42 (d), 49.65 (d), 62.08 (t), 62.19 (t), 69.62 (t), 121.67 (t), 131.71 (s), 167.13 (s), 167.48 (s), 175.08 (s). Selected HMBC correlations are between \( \delta \) 3.87 (H-4) and \( \delta \) 42.87 (C-3), 121.67 (=CH\(_2\)), between \( \delta \) 3.40 (H-3) and \( \delta \) 47.42 (C-4), 131.71 (CBr=), \( \delta \) 4.49 (H-5b) and \( \delta \) 42.87 (C-3), 131.71 (CBr=), and between \( \delta \) 5.57, 5.82 (=CH\(_2\)) and \( \delta \) 47.42 (C-4), 131.71 (CBr=); IR (neat) 2983, 1780, 1733, 1627, 1475, 1373, 1179, 1032 cm\(^{-1}\); MS (CI) \( m/z \) 351, 349 (M+H\(^+\)); HRMS (M+H\(^+\)) \( m/z \) 349.0285, 351.0261 (calcd for C\(_{13}\)H\(_{18}\)BrO\(_6\)) 349.0287, 351.0266).

Diethyl 2-[Trans-4-(1-chloro-2-methylprop-1-enyl)-2-oxotetrahydrofuran-3-yl]malonate (4c): \( R_f = 0.4 \) (hexane-ether = 1 : 1); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 1.28 (t, \( J = 7.1 \) Hz, 3H), 1.29 (t, \( J = 7.1 \) Hz, 3H), 1.79 (s, 3H), 1.86 (s, 3H), 3.56 (dd, \( J = 10.4, 4.8 \) Hz, 1H), 3.96 (d, \( J = 4.6 \) Hz, 1H), 4.01-4.26 (m, 5H), 4.39 (dd, \( J = 8.6, 8.6 \) Hz, 1H), 4.49 (ddd, \( J = 10.4, 8.9 \), 8.9 Hz, 1H). Selected NOEs are between \( \delta \) 4.49 (H-4) and \( \delta \) 3.96 (CH(CO\(_2\)Et))\(_2\)).; \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (ppm) 13.94 (q), 14.01 (q), 20.82 (q), 22.65 (q), 41.08 (d), 42.53 (d), 49.28 (d), 61.98 (t), 62.03 (t),
Selected HMBC correlations are between $\delta$ 4.49 (H-4) and $\delta$ 42.53 (C-3), 68.53 (C-5), between $\delta$ 3.56 (H-3) and $\delta$ 41.08 (C-4), 123.71 (CCl=), $\delta$ 4.39 (H-5b) and $\delta$ 42.53 (C-3), 68.53 (C-5), and between $\delta$ 1.79, 1.86 (=C=C(CH$_3$)$_2$) and $\delta$ 123.71 (CCl=); IR (neat) 2983, 2920, 1782, 1738, 1466, 1446, 1374, 1239, 1179, 1027 cm$^{-1}$; MS (EI) $m/z$ 334 (M$^+$, 5.6), 332 (M$^+$, 16), 173 (20), 160 (19), 85 (81), 83 (100%); HRMS M$^+$ 332.1026, 334.1010 (caled for C$_{15}$H$_{21}$ClO$_6$ 332.1027, 334.0997).

**Diethyl 2-[Trans-4-(1-bromo-2-methylprop-1-enyl)-2-oxotetrahydrofuran-3-yl]malonate (4d):** $R_f$ = 0.5 (hexane-ether = 1 : 1); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.29 (t, $J$ = 7.1 Hz, 6H), 1.82 (s, 3H), 1.89 (s, 3H), 3.58 (dd, $J$ = 9.9, 4.7 Hz, 1H), 3.96 (d, $J$ = 4.7 Hz, 1H), 4.01-4.27 (m, 5H), 4.35-4.43 (m, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 13.98 (q), 14.02 (q), 21.36 (q), 26.41 (q), 42.17 (d), 43.81 (d), 49.22 (d), 62.00 (t), 62.03 (t), 69.49 (t), 119.05 (s), 137.31 (s), 167.51 (s), 167.73 (s), 175.52 (s); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ (ppm) 0.892 (t, $J$ = 7.1 Hz, 3H), 0.907 (t, $J$ = 7.1 Hz, 3H), 1.53 (s, 3H), 1.57 (s, 3H), 3.51 (dd, $J$ = 10.7, 4.9 Hz, 1H), 3.69-4.00 (m, 6H), 4.08 (d, $J$ = 4.9 Hz, 1H), 4.44 (ddd, $J$ = 10.7, 8.9, 8.9 Hz, 1H). Selected NOEs are between $\delta$ 4.44 (H-4) and $\delta$ 4.08 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, C$_6$D$_6$) $\delta$ (ppm) 13.77 (q), 13.78 (q), 21.06 (q), 25.78 (q), 42.35 (d), 44.01 (d), 49.55 (d), 61.61 (t), 61.78 (t), 69.89 (t), 119.68 (s), 136.80 (s), 167.66 (s), 168.00 (s), 174.81 (s). Selected HMBC correlations are between $\delta$ 3.51 (H-3) and $\delta$ 49.55 (CH(CO$_2$Et)$_2$), 42.35...
(C-4), between $\delta$ 4.44 (H-4) and $\delta$ 49.55 (CH(CO$_2$Et)$_2$), 44.01 (C-3), 69.89 (C-5), between $\delta$ 4.08 (CH(CO$_2$Et)$_2$) and $\delta$ 44.01 (C-3), 42.35 (C-4), and between $\delta$ 1.53, 1.57 (=C(CH$_3$)$_2$) and $\delta$ 119.68 (CBr=); IR (neat) 2983, 2913, 1781, 1735, 1446, 1373, 1297, 1265, 1236, 1187, 1027 cm$^{-1}$; MS (EI) $m/z$ 378 ($M^+$, 9.3), 376 ($M^+$, 9.3), 333 (14), 331 (14), 297 (100%); HRMS $M^+$ 376.0519, 378.0499 (calcd for C$_{15}$H$_{21}$BrO$_6$ 376.0522, 378.0501).

**Diethyl 2-(Cis-4-ethynyl-2-oxotetrahydrofuran-3-yl)malonate (5):**

$R_f = 0.5$ (hexane-ether = 1 : 1);

pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.29 (t, $J = 7.1$ Hz, 3H), 1.32 (t, $J = 7.1$ Hz, 3H), 2.29 (d, $J = 2.6$ Hz, 1H), 3.55 (dd, $J = 10.4$, 8.3 Hz, 1H), 3.76 (dddd, $J = 8.3$, 4.4, 3.4, 2.6 Hz, 1H), 3.87 (d, $J = 10.4$ Hz, 1H), 4.22-4.33 (m, 4H), 4.40 (d, $J = 4.4$ Hz, 1H), 4.41 (d, $J = 3.4$ Hz, 1H); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ (ppm) 0.890 (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J = 7.1$ Hz, 3H), 1.63 (d, $J = 2.6$ Hz, 1H), 3.15 (dddd, $J = 8.2$, 5.7, 2.6, 1.5 Hz, 1H), 3.25 (dd, $J = 8.9$, 5.7 Hz, 1H), 3.42 (dd, $J = 10.8$, 8.2 Hz, 1H), 3.68 (dd, $J = 8.9$, 1.5 Hz, 1H), 2.92 (q, $J = 7.1$ Hz, 2H), 4.09 (d, $J = 10.8$ Hz, 1H), 4.11-4.25 (m, 2H). Selected NOEs are between $\delta$ 3.15 (H-4) and $\delta$ 3.42 (H-3), 3.25 (H-5a) and between $\delta$ 3.42 (H-3) and $\delta$ 4.09 (CH(CO$_2$Et)$_2$); $^1$C NMR (100.6 MHz, C$_6$D$_6$) $\delta$ (ppm) 13.83 (q), 13.93 (q), 31.79 (d), 43.07 (d), 51.41 (d), 61.92 (t), 62.12 (t), 70.46 (t), 74.16 (d), 79.65 (s), 167.38 (s), 167.44 (s), 173.81 (s). Selected
HMBC correlations are between \( \delta 3.42 \) (H-3) and \( \delta 51.41 \) (CH), between \( \delta 3.15 \) (H-4) and \( \delta 43.07 \) (C-3), 79.65 (C=CH), between \( \delta 3.68 \) (H-5b) and \( \delta 31.79 \) (C-4), 43.07 (C-3), 79.65 (C=CH) and between \( \delta 3.25 \) (H-5a) and \( \delta 79.65 \) (C=CH); IR (neat) 3275, 2982, 1781, 1467, 1447, 1370, 1283, 1249, 1163, 1096, 1029 cm\(^{-1}\); MS (EI) \( m/z \) 269 ((M+H), 83), 223 (100%); HRMS (M+H)\(^+\) 269.1029 (calcd for C\(_{13}\)H\(_{17}\)O\(_6\) 269.1025).

6: \( R_f = 0.3 \) (hexane-ether = 1 : 1); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 1.29 (t, \( J = 7.1 \) Hz, 3H), 1.30 (t, \( J = 7.1 \) Hz, 3H), 3.54 (d, \( J = 7.0 \) Hz, 1H), 3.96 (d, \( J = 4.1 \) Hz, 1H), 4.21-4.30 (m, 4H), 4.70 (dtd, \( J = 7.2, 2.3, 1.3 \) Hz, 1H), 4.74 (dd, \( J = 7.0, 4.1 \) Hz, 1H), 4.87 (dt, \( J = 6.6, 2.2 \) Hz, 2H), 5.29 (tt, \( J = 7.0, 6.6 \) Hz, 1H); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (ppm) 14.01 (q), 14.04 (q), 55.14 (d), 62.05 (t), 62.09 (t), 63.89 (t), 69.75 (d), 76.92 (t), 85.67 (d), 166.99 (s), 167.19 (s), 171.45 (s), 210.13 (s); IR (neat) 3491, 2984, 1958, 1739, 1466, 1446, 1373, 1267, 1178, 1033 cm\(^{-1}\); MS (Cl) \( m/z \) 287 (M+H\(^+\)); HRMS (M+H)\(^+\) 287.1130 (calcd for C\(_{13}\)H\(_{19}\)O\(_7\) 287.1131).

**Diethyl 2-(Trans-4-ethyl-2-oxotetrahydrofuran-3-yl)malonate (7)**

A mixture of 4a (168 mg, 0.55 mmol) and 10% Pd–C (59 mg, 10 mol%) in methanol (5.5 mL) was stirred in a hydrogen atmosphere for 18 h at room temperature. The catalyst was removed by filtration (Celite) and washed with methanol. The filtrate was concentrated in vacuo. The residue was purified
by column chromatography over silica gel with hexane-ether as eluent to give 7 (76 mg, 51%); $R_f = 0.4$ (hexane-ether = 1 : 1); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 0.917 (t, $J = 7.5$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.37-1.50 (m, 1H), 1.61-1.71 (m, 1H), 2.60 (dddd, $J = 9.2$, 9.0, 8.4, 7.9, 4.6 Hz, 1H), 2.87 (dd, $J = 9.0$, 4.8 Hz, 1H), 3.90 (d, $J = 4.8$ Hz, 1H), 3.92 (dd, $J = 9.0$, 7.9 Hz, 1H), 4.20-4.30 (m, 4H), 4.52 (dd, $J = 9.0$, 8.4 Hz, 1H). Selected NOEs are between $\delta$ 2.87 (H-3) and $\delta$ 0.917 (CH$_2$CH$_3$), 1.37-1.50, 1.61-1.71 (CH$_2$CH$_3$), and between $\delta$ 2.60 (H-4) and $\delta$ 3.90 (CH(CO$_2$Et)$_2$, overlapped); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 11.12 (q), 14.01 (q), 14.05 (q), 26.23 (t), 39.34 (d), 44.79 (d), 51.04 (d), 62.01 (t), 62.07 (t), 71.91 (t), 167.49 (s), 167.71 (s), 176.76 (s). Selected HMBC correlations are between $\delta$ 1.37-1.50, 1.61-1.71 (CH$_2$CH$_3$) and $\delta$ 44.79 (C-3), 39.34 (C-4), 71.91 (C-5) and between $\delta$ 0.917 (CH$_2$CH$_3$) and $\delta$ 39.34 (C-4); IR (neat) 2980, 1778, 1733, 1465, 1372, 1300, 1264, 1235, 1178, 1026 cm$^{-1}$; MS (EI) m/z 273 ((M+H)$^+$, 3.8), 272 (M$^+$, 1.9), 227 (51), 160 (100%); HRMS (M+H)$^+$ 273.1331 (calcd for C$_{13}$H$_{21}$O$_6$ 273.1338), M$^+$ 272.1259 (calcd for C$_{13}$H$_{20}$O$_6$ 272.1260).

**Transformation of 8 to 7**

A solution of compound 8 (113 mg, 0.37 mmol), Bu$_3$SnH (215 mg, 199 $\mu$L, 0.74 mmol), and AIBN (12.2 mg, 0.074 mmol) in benzene (2.3 mL) was heated at reflux for 3 h and cooled to room temperature. The reaction mixture was concentrated under reduced pressure. The residue was purified.
by column chromatography over silica gel with hexane-ether as the eluent to give 7 (89 mg, 89%).

**Diethyl 2-(Cis-4-ethyl-2-oxotetrahydrofuran-3-yl)malonate (7-cis)**

A mixture of 5 (146 mg, 0.54 mmol) and 10% Pd–C (58 mg, 10 mol%) in methanol (5.5 mL) was stirred in a hydrogen atmosphere for 18 h at room temperature. The catalyst was removed by filtration (Celite) and washed with methanol. The filtrate was concentrated *in vacuo*. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give 7-cis (115 mg, 78%);

Rf = 0.3 (hexane-ether = 1 : 1); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 0.951 (t, $J = 7.3$ Hz, 3H), 1.19-1.33 (m, 1H), 1.29 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.34-1.44 (m, 1H), 2.63-2.70 (m, 1H), 3.57-3.58 (m, 2H), 4.19-4.32 (m, 6H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 11.36 (q), 13.97 (q), 14.04 (q), 20.34 (t), 39.63 (d), 43.83 (d), 49.37 (d), 62.16 (t), 70.13 (t), 167.28 (s), 167.38 (s), 175.86 (s); $^1$H NMR (400 MHz, C$_6$D$_6$) δ (ppm) 0.451 (t, $J = 7.4$ Hz, 3H), 0.698-0.814 (m, 1H), 0.881 (t, $J = 7.1$ Hz, 3H), 0.918-1.02 (m, 1H), 1.06 (t, $J = 7.1$ Hz, 3H), 2.18 (m, 1H), 3.49 (ddd, $J = 9.3, 5.3, 1.1$ Hz, 1H), 3.56 (dd, $J = 11.4, 7.3$ Hz, 1H), 3.57 (dd, $J = 9.3, 1.3$ Hz, 1H), 3.65 (d, $J = 11.4$ Hz, 1H), 3.86-3.93 (m, 2H), 4.10-4.23 (m, 2H). Selected NOEs are between δ 3.65 (CH(CO$_2$Et)$_2$) and δ 0.698-0.814, 0.918-1.02 (CH$_2$CH$_3$); $^{13}$C NMR (100.6 MHz, C$_6$D$_6$) δ (ppm) 11.08 (q), 13.86 (q), 13.96 (q), 20.27 (t), 39.60 (d), 44.11 (d), 49.76 (d), 61.78 (t), 61.97 (t), 69.47 (t), 167.51 (s), 167.61 (s), 175.46 (s). Selected HMBC correlations are between δ 3.65 (CH(CO$_2$Et)$_2$), 3.49 (H-5) and δ 44.11
between $\delta$ 0.451 ($CH_2CH_3$), 0.698-0.814 ($CHHCH_3$) and $\delta$ 39.60 (C-4), and between $\delta$ 0.698-0.814, 0.918-1.02 ($CH_2CH_3$) and $\delta$ 69.47 (C-5); IR (neat) 2979, 1777, 1752, 1737, 1465, 1369, 1284, 1166, 1030 cm$^{-1}$; MS (EI) $m/z$ 272 (M$^+$, 1.9), 271 (11), 226 (100%); HRMS M$^+$ 272.1273 (calcd for C$_{13}$H$_{20}$O$_6$ 272.1260).

Allenylamine **10a** was prepared according to the literature,$^{19}$ and **10b** was also prepared according to the same procedure.

**10b**; pale yellow oil; bp. 43 °C/50 mmHg; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 0.925 (t, $J$ = 7.3 Hz, 3H), 1.38 (bs, 1H), 1.52 (qt, $J$ = 7.3, 7.3 Hz, 2H), 2.61 (t, $J$ = 7.3 Hz, 2H), 3.25 (dt, $J$ = 6.4, 3.1 Hz, 2H), 4.76 (dt, $J$ = 6.6, 3.1 Hz, 2H), 5.22 (tt, $J$ = 6.6, 6.4 Hz, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 11.87 (q), 23.22 (t), 47.92 (t), 51.19 (t), 75.92 (t), 89.44 (d), 208.35 (s); IR (neat) 3301, 2958, 2931, 2874, 1955, 1458, 1127, 842 cm$^{-1}$; MS (CI) $m/z$ 112 (M+H)$^+$; HRMS (M+H)$^+$ 112.1132 (calcd for C$_7$H$_{14}$N 112.1126).

**Preparation of Substrates 11a-b**

To a solution of 1,1-diethyl 2-hydrogen thenetericarboxylate (432 mg, 2 mmol) (prepared from 1,1-diethyl 2-tert-butyl thenetericarboxylate (545 mg, 2 mmol) upon treatment with CF$_3$CO$_2$H) in THF (2.8 mL) were added allenylamine **10a** (326 mg, 2 mmol), Et$_3$N (0.28 mL, 202 mg, 2 mmol),
HOBt (1-hydroxybenzotriazole) (540 mg, 4 mmol) and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (399 mg, 2.08 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, and was allowed to warm to room temperature and stirred overnight. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH₂Cl₂. The organic phase was washed with saturated aqueous NaHCO₃ solution, 2 M aqueous citric acid, saturated aqueous NaHCO₃ and water, dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ether (1 : 1) to give 11a (375 mg, 53%); Rᶠ = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) (2 rotamers, ratio 1.5 : 1) δ (ppm) 1.29 (t, J = 7.1, 3H×0.4, minor rotamer) 1.31 (t, J = 7.1 Hz, 3H×0.6, major rotamer), 1.32 (t, J = 7.1 Hz, 3H×0.6), 1.35 (t, J = 7.1 Hz, 3H×0.4), 3.85 (dt, J = 6.0, 3.1 Hz, 1H×0.6), 4.00 (dt, J = 6.8, 2.5 Hz, 1H×0.4), 4.24-4.39 (m, 4H), 4.57 (s, 2H×0.4), 4.65 (s, 2H×0.6), 4.78 (dt, J = 6.6, 2.6 Hz, 2H×0.4), 4.88 (dt, J = 6.6, 3.1 Hz, 2H×0.6), 5.07 (tt, J = 6.6, 6.0 Hz, 1H×0.6), 5.15 (tt, J = 6.8, 6.6 Hz, 1H×0.4), 5.24-7.43 (m, 5H), 7.34 (s, 1H×0.4), 7.36 (s, 1H×0.6); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 14.01 (q), 14.03 (q), 14.05 (q), 14.10 (q), 43.85 (t), 45.88 (t), 48.37 (t), 51.01 (t), 61.95 (t), 62.25 (t), 76.58 (t), 78.11 (t), 85.59 (d), 86.58 (d), 127.22 (d), 127.75 (d), 128.10 (d), 128.57 (d), 128.72 (d), 129.05 (d), 134.19 (d), 134.28 (d), 135.20 (s), 135.54 (s), 135.71 (s), 136.46 (s), 162.97 (s), 163.08 (s), 164.26 (s), 164.34 (s), 164.52 (s), 208.90 (s), 209.69 (s); IR (neat) 2983, 1956, 1732, 1656, 1496, 1446, 1373, 1255, 1199, 1069, 1022 cm⁻¹; MS (EI) m/z 357
(M⁺, 67), 312 (24), 158 (30), 143 (73), 91 (100%); HRMS M⁺ 357.1577 (calcd for C₂₀H₂₃NO₅
357.1576).

**11b** (82%): Rₓ = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) (2 rotamers, ratio 1 : 1) δ (ppm) 0.909 (t, J = 7.4, 3H×0.5) 0.930 (t, J = 7.4 Hz, 3H×0.5), 1.318 (t, J = 7.1 Hz, 3H×0.5), 1.320 (t, J = 7.1 Hz, 3H×0.5), 1.322 (t, J = 7.1 Hz, 3H×0.5), 1.324 (t, J = 7.1 Hz, 3H×0.5), 1.55-1.68 (m, 2H), 3.30 (dd, J = 7.6, 7.6 Hz, 2H×0.5), 3.34-3.38 (m, 2H×0.5), 3.94 (ddd, J = 6.1, 3.1, 3.1 Hz, 2H×0.5), 4.02 (ddd, J = 6.6, 2.7, 2.7 Hz, 2H×0.5), 4.26-4.36 (m, 4H), 4.80 (dt, J = 6.6, 2.7 Hz, 2H×0.5), 4.89 (dt, J = 6.6, 3.1 Hz, 2H×0.5), 5.12-5.20 (m, 1H), 7.32 (s, 1H×0.5), 7.33 (s, 1H×0.5); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 11.21 (q), 11.36 (q), 13.95 (q×2), 14.01 (q), 14.03 (q), 20.68 (t), 22.12 (t), 44.37 (t), 47.01 (t), 47.73 (t), 49.59 (t), 61.78 (t×2), 62.11 (t), 62.19 (t), 76.47 (t), 78.06 (t), 86.07 (d), 87.08 (d), 133.94 (d), 134.55 (d), 134.60 (s), 135.05 (s), 163.08 (s), 163.11 (s), 163.62 (s), 163.91 (s), 164.58 (s), 164.62 (s), 208.74 (s), 209.33 (s); IR (neat) 2967, 2937, 1956, 1729, 1652, 1466, 1445, 1430, 1256, 1068 cm⁻¹; MS (EI) m/z 309 (M⁺, 43), 199 (48), 171 (63), 143 (100%); HRMS M⁺ 309.1581 (calcd for C₁₆H₂₃NO₅ 309.1576).

Diethyl 2-(1-Benzyl-trans-4-(1-chlorovinyl)-2-oxopyrrolidin-3-yl)malonate (12a): Typical
Experimental Procedure (Table 3-2, entry 2)

- 54 -
To a solution of 11a (179 mg, 0.5 mmol) in CH₂Cl₂ (2 mL) was added ZnCl₂ (68.2 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by water and then saturated aqueous NaHCO₃. The mixture was extracted with dichloromethane and the organic phase was dried (Na₂SO₄), and evaporated in vacuo. The crude product included impurities (possibly non-cyclized water-adducts). To a solution of the crude product in CH₂Cl₂ (2 mL) was added ZnCl₂ (68.2 mg, 0.5 mmol). The mixture was stirred at room temperature for 18 h. The reaction mixture was quenched by water and then saturated aqueous NaHCO₃. The mixture was extracted with dichloromethane and the organic phase was dried (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane-ether (1 : 2) as eluent to give 12a (148 mg, 76%); Rf = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.275 (t, J = 7.1 Hz, 3H), 1.279 (t, J = 7.1 Hz, 3H), 3.29 (dd, J = 9.7, 7.1 Hz, 1H), 3.36 (dd, J = 9.0, 4.7 Hz, 1H), 3.36 (dd, J = 9.0, 4.7 Hz, 1H), 3.41 (dd, J = 9.7, 9.4 Hz, 1H), 3.72 (ddd, J = 9.4, 9.0, 7.1 Hz, 1H), 4.06 (d, J = 4.7 Hz, 1H), 4.11-4.25 (m, 4H), 4.40 (d, J = 14.9 Hz, 1H), 4.58 (d, J = 14.9 Hz, 1H), 5.19 (d, J = 1.5 Hz, 1H), 5.25 (d, J = 1.5 Hz, 1H), 7.24-7.36 (m, 5H). Selected NOEs are between δ 3.36 (H-3) and δ 5.25 (=CHH) and between δ 3.72 (H-4) and δ 4.06 (CH₂CO₂Et₂).; ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 13.98 (q), 14.04 (q), 42.64 (d), 44.58 (d), 46.76 (t), 48.64 (t), 50.09 (d), 61.67 (t), 61.69 (t), 115.41 (t), 127.72 (d), 128.05 (d), 128.76 (d), 135.80 (s), 141.52 (s), 167.98 (s), 168.14 (s), 171.88 (s). Selected HMBC correlations are between δ 3.36 (H-3) and δ 50.09
(CH(CO₂Et)₂), 42.64 (C-4), between δ 3.72 (H-4) and δ 50.09 (CH(CO₂Et)₂), 44.58 (C-3), between δ 3.29, 3.41 (H-5a,5b) and δ 141.52 (CCl=CH₂), and between δ 4.06 (CH(CO₂Et)₂) and δ 44.58 (C-3), 42.64 (C-4); IR (neat) 2982, 2935, 1732, 1697, 1632, 1491, 1446, 1373, 1261, 1175, 1032 cm⁻¹; MS (EI) m/z 395 (M⁺, 8.8), 393 (M⁺, 26), 234 (54), 91 (100%); HRMS M⁺ 393.1341, 395.1317 (calcd for C₂₀H₂₄ClNO₅ 393.1345, 395.1314).

Diethyl 2-(1-Benzyl-trans-4-(1-bromovinyl)-2-oxopyrrolidin-3-yl)malonate (12b): Rf = 0.6 (ether); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.26 (dd, J = 9.8, 7.1 Hz, 1H), 3.34 (dd, J = 8.7, 4.7 Hz, 1H), 3.39 (dd, J = 9.8, 9.1 Hz, 1H), 3.63 (ddd, J = 9.1, 8.7, 7.1 Hz, 1H), 4.07 (d, J = 4.7 Hz, 1H), 4.11-4.25 (m, 4H), 4.40 (d, J = 14.9 Hz, 1H), 4.59 (d, J = 14.9 Hz, 1H), 5.43 (d, J = 1.8 Hz, 1H), 5.70 (d, J = 1.8 Hz, 1H), 7.25-7.36 (m, 5H). Selected NOEs are between δ 3.34 (H-3) and δ 5.70 (=CHH) and between δ 3.63 (H-4) and δ 4.07 (CH(CO₂Et)₂); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 14.01 (q), 14.04 (q), 43.97 (d), 45.50 (d), 46.76 (t), 49.54 (t), 49.99 (d), 61.68 (t), 61.70 (t), 119.86 (t), 127.71 (d), 128.06 (d), 128.75 (d), 134.80 (s), 135.77 (s), 168.00 (s), 168.11 (s), 171.78 (s). Selected HMBC correlations are between δ 3.34 (H-3) and δ 43.97 (C-4), between δ 3.63 (H-4) and δ 49.99 (CH(CO₂Et)₂), 45.50 (C-3), between δ 3.26, 3.39 (H-5a,5b) and δ 134.80 (CBr=CH₂), and between δ 4.07 (CH(CO₂Et)₂) and δ 45.50 (C-3), 43.97 (C-4); IR (neat) 2982, 1733, 1699, 1627, 1490, 1446, 1373, 1290, 1263, 1176, 1030 cm⁻¹; MS
Diethyl 2-(1-Benzyl-trans-4-(1-iodovinyl)-2-oxopyrrolidin-3-yl)malonate (12c): $R_f = 0.6$

(hexane-ether = 1 : 4); yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.28 (t, $J = 7.1$ Hz, 3H), 1.30 (t, $J = 7.1$ Hz, 3H), 3.10-3.17 (m, 2H), 3.21 (dd, $J = 8.6$, 4.5 Hz, 1H), 3.35 (m, 1H), 4.06 (d, $J = 4.5$ Hz, 1H), 4.08-4.25 (m, 4H), 4.39 (d, $J = 14.8$ Hz, 1H), 4.59 (d, $J = 14.8$ Hz, 1H), 5.74 (d, $J = 1.6$ Hz, 1H), 6.19 (dd, $J = 1.6$, 0.4 Hz, 1H), 7.25-7.30 (m, 3H), 7.32-7.36 (m, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 14.02 (q), 14.06 (q), 46.08 (d), 46.72 (t), 47.11 (d), 49.87 (d), 51.12 (t), 61.64 (t), 61.66 (t), 115.84 (s), 127.69 (d), 128.08 (d), 128.54 (t), 128.70 (d), 135.73 (s), 167.98 (s), 168.03 (s), 171.63 (s); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ (ppm) 0.934 (t, $J = 7.1$ Hz, 3H), 0.955 (t, $J = 7.1$ Hz, 3H), 2.86 (dd, $J = 9.8$, 7.1 Hz, 1H), 2.98 (dd, $J = 9.8$, 8.8 Hz, 1H), 3.20 (ddd, $J = 8.8$, 8.8, 7.1 Hz, 1H), 3.30 (dd, $J = 8.8$, 4.9 Hz, 1H), 3.83-4.08 (m, 4H), 4.06 (d, $J = 15.0$ Hz, 1H), 4.31 (d, $J = 4.9$ Hz, 1H), 4.51 (d, $J = 15.0$ Hz, 1H), 5.41 (d, $J = 1.6$ Hz, 1H), 5.81 (dd, $J = 1.6$, 0.6 Hz, 1H), 7.04-7.09 (m, 1H), 7.14-7.21 (m, 4H). Selected NOEs are between $\delta$ 3.30 (H-3) and $\delta$ 5.81 (=CHH) and between $\delta$ 3.20 (H-4) and $\delta$ 4.31 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, C$_6$D$_6$) $\delta$ (ppm) 13.90 (q), 13.95 (q), 46.45 (d), 46.54 (t), 47.24 (d), 50.23 (d), 50.83 (t), 61.39 (t), 61.48 (t), 116.56 (s), 127.69 (d), 128.31 (d), 128.38 (t), 128.81 (d), 136.69 (s), 168.15 (s), 168.29 (s), 171.23 (s). Selected HMBC correlations are between...
δ 3.30 (H-3) and δ 50.23 (CH(CO₂Et)₂), 46.45 (C-4), between δ 3.20 (H-4) and δ 50.23 (CH(CO₂Et)₂), 47.24 (C-3), between δ 2.86, 2.98 (H-5a,5b) and δ 116.56 (Cl=CH₂), and between δ 4.31 (CH(CO₂Et)₂) and δ 47.24 (C-3), 46.45 (C-4).; IR (neat) 2980, 2934, 1733, 1699, 1612, 1488, 1445, 1372, 1287, 1261, 1175, 1030 cm⁻¹; MS (FAB) m/z 508 (M+Na)⁺, 486 (M+H)⁺; HRMS (M+H)⁺ 486.0779 (calcd for C₂₀H₂₅INO₅ 486.0778).

Diethyl 2-(Trans-4-(1-chlorovinyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (12d): Rᵣ = 0.5 (hexane-ether = 1 : 2); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 0.912 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.57 (qt, J = 7.3, 7.3 Hz, 2H), 3.21-3.33 (m, 3H), 3.40 (dd, J = 9.7, 7.0 Hz, 1H), 3.54 (dd, J = 9.7, 9.4 Hz, 1H), 3.74 (ddd, J = 8.8, 8.8, 7.0 Hz, 1H), 4.01 (d, J = 4.6 Hz, 1H), 4.09-4.25 (m, 4H), 5.22 (d, J = 1.5 Hz, 1H), 5.30 (d, J = 1.5 Hz, 1H). Selected NOEs are between δ 3.21-3.33 (H-3, overlapped) and δ 5.30 (=CHH) and between δ 3.74 (H-4) and δ 4.01 (CH(CO₂Et)₂); ¹³C NMR (100.6 MHz, CDCl₃) δ (ppm) 11.18 (q), 13.95 (q), 13.99 (q), 20.32 (t), 42.57 (d), 44.37 (t), 44.71 (d), 49.15 (t), 50.12 (d), 61.56 (t), 61.62 (t), 115.22 (t), 141.81 (s), 167.97 (s), 168.22 (s), 171.63 (s). Selected HMBC correlations are between δ 3.21-3.33 (H-3, overlapped) and δ 50.12 (CH(CO₂Et)₂), 42.57 (C-4), between δ 3.74 (H-4) and δ 50.12 (CH(CO₂Et)₂), 44.71 (C-3), between δ 3.40, 3.54 (H-5a,5b) and δ 141.81 (CCl=CH₂), and between δ 4.01 (CH(CO₂Et)₂) and δ 44.71 (C-3), 42.57 (C-4); IR (neat) 2966, 2936, 1733, 1696, 1632, 1491, 1446, 1373, 1264, 1175,
Diethyl 2-(Trans-4-(1-bromovinyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (12e): \( R_f = 0.6 \) (ether); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) (ppm) 0.915 (t, \( J = 7.3 \) Hz, 3H), 1.27 (t, \( J = 7.1 \) Hz, 3H), 1.28 (t, \( J = 7.1 \) Hz, 3H), 1.57 (qt, \( J = 7.3, 7.3 \) Hz, 1H), 3.20-3.34 (m, 3H), 3.38 (dd, \( J = 9.7, 6.8 \) Hz, 1H), 3.53 (dd, \( J = 9.7, 8.7 \) Hz, 1H), 3.65 (ddd, \( J = 8.7, 8.7, 6.8 \) Hz, 1H), 4.01 (d, \( J = 4.6 \) Hz, 1H), 4.09-4.25 (m, 4H), 5.47 (d, \( J = 1.8 \) Hz, 1H), 5.74 (dd, \( J = 1.8, 0.4 \) Hz, 1H). Selected NOEs are between \( \delta 3.20-3.34 \) (H-3, overlapped) and \( \delta 5.74 \) (=CHH) and between \( \delta 3.65 \) (H-4) and \( \delta 4.01 \) (CH(CO\(_2\)Et))\(_2\)); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (ppm) 11.18 (q), 13.98 (q), 20.31 (t), 43.90 (d), 44.36 (t), 45.63 (d), 50.04 (d), 50.08 (t), 61.55 (t), 61.61 (t), 119.64 (t), 135.10 (s), 167.96 (s), 168.17 (s), 171.53 (s). Selected HMBC correlations are between \( \delta 3.20-3.34 \) (H-3, overlapped) and \( \delta 50.04 \) (CH(CO\(_2\)Et))\(_2\), between \( \delta 3.65 \) (H-4) and \( \delta 50.04 \) (CH(CO\(_2\)Et))\(_2\), 45.63 (C-3), between \( \delta 3.38, 3.53 \) (H-5a,5b) and \( \delta 135.10 \) (CBr=CH\(_2\)), and between \( \delta 4.01 \) (CH(CO\(_2\)Et))\(_2\) and \( \delta 45.63 \) (C-3), 43.90 (C-4); IR (neat) 2966, 2935, 1733, 1698, 1627, 1490, 1446, 1372, 1287, 1264, 1160, 1043 cm\(^{-1}\); MS (EI) \( m/z \) 391 (M\(^+\), 38), 389 (M\(^+\), 36), 346 (27), 344 (29), 310 (100) 232 (96), 230 (99%); HRMS M\(^+\) 389.0836, 391.0811 (calcd for C\(_{16}\)H\(_{23}\)BrNO\(_5\) 389.0838, 391.0817).
Diethyl 2-(Trans-4-(1-iodovinyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (12f): R<sub>f</sub> = 0.6
(hexane-ether = 1 : 4); yellow oil; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ (ppm) 0.921 (t, J = 7.3 Hz, 3H), 1.27 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.57 (qt, J = 7.3, 7.3 Hz, 2H), 3.11-3.34 (m, 5H), 3.49 (ddd, J = 9.4, 8.4, 1.0 Hz, 1H), 4.01 (d, J = 4.4 Hz, 1H), 4.08-4.25 (m, 4H), 5.77 (d, J = 1.6 Hz, 1H), 6.23 (dd, J = 1.6, 0.5 Hz, 1H); <sup>1</sup>C NMR (100.6 MHz, CDCl<sub>3</sub>) δ (ppm) 11.24 (q), 13.98 (q), 14.04 (q), 20.32 (t), 44.36 (t), 46.00 (d), 47.26 (d), 49.92 (d), 51.71 (t), 61.56 (t), 61.62 (t), 116.18 (s), 128.36 (t), 167.99 (s), 168.14 (s), 171.43 (s); <sup>1</sup>H NMR (400 MHz, C<sub>6</sub>D<sub>6</sub>) δ (ppm) 0.758 (t, J = 7.3 Hz, 3H), 0.914 (t, J = 7.1 Hz, 3H), 0.945 (t, J = 7.1 Hz, 3H), 1.27 (qt, J = 7.3, 7.3 Hz, 2H), 2.92 (dd, J = 9.7, 6.8 Hz, 1H), 3.01-3.10 (m, 3H), 3.22 (dd, J = 8.4, 4.8 Hz, 1H), 3.27 (dddd, J = 8.4, 8.1, 6.8, 0.5 Hz, 1H), 3.84-4.04 (m, 4H), 4.28 (d, J = 4.8 Hz, 1H), 5.47 (d, J = 1.6 Hz, 1H), 5.93 (dd, J = 1.6, 0.5 Hz, 1H).
Selected NOEs are between δ 3.22 (H-3, overlapped) and δ 5.93 (=CHH) and between δ 3.27 (H-4, overlapped) and δ 4.28 (CH(CO<sub>2</sub>Et)<sub>2</sub>); <sup>1</sup>C NMR (100.6 MHz, C<sub>6</sub>D<sub>6</sub>) δ (ppm) 11.26 (q), 13.88 (q), 13.95 (q), 20.50 (t), 44.18 (t), 46.33 (d), 47.42 (d), 50.29 (d), 51.48 (t), 61.36 (t), 61.39 (t), 117.08 (s), 128.11 (t), 168.27 (s), 168.29 (s), 171.10 (s). Selected HMBC correlations are between δ 3.22 (H-3) and δ 50.29 (CH(CO<sub>2</sub>Et)<sub>2</sub>), 117.08 (CI=CH<sub>2</sub>), between δ 3.27 (H-4) and δ 51.48 (C-5), between δ 2.86, 2.98 (H-5a,5b) and δ 46.33 (C-4), and between δ 4.28 (CH(CO<sub>2</sub>Et)<sub>2</sub>) and δ 47.42 (C-3), 46.33 (C-4).
IR (neat) 2966, 2934, 1733, 1695, 1612, 1489, 1446, 1372, 1287, 1175, 1112, 1043 cm<sup>-1</sup>; MS (EI) m/z 437 (M<sup>+</sup>, 38), 392 (38), 310 (100%); HRMS M<sup>+</sup> 437.0697 (calcd for C<sub>16</sub>H<sub>24</sub>INO<sub>5</sub> 437.0699).
**Trans-3-(di(ethoxycarbonyl)methyl)-2-oxotetrahydrofuran-4-carboxylic acid (13):**

Compound 4a (84 mg, 0.28 mmol) was dissolved in a mixture of CH$_3$CN (1.4 mL), CCl$_4$ (1.4 mL), and H$_2$O (1.4 mL). NaIO$_4$ (385 g, 1.8 mmol) was then added followed by RuCl$_3$·xH$_2$O (5.2 mg, ca. 0.025 mmol). After 1 h of stirring at room temperature, the solution was diluted with CH$_2$Cl$_2$. The layers were separated, and the aqueous layer was extracted with CH$_2$Cl$_2$ three times. The combined organic layers were dried (Na$_2$SO$_4$) and concentrated *in vacuo*. The residue was filtered through a short plug of Cerite that was washed with ether to give 13 (78 mg, 98%); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.28 (t, $J$ = 7.1 Hz, 3H), 1.29 (t, $J$ = 7.1 Hz, 3H), 3.52 (dd, $J$ = 9.2, 4.4 Hz, 1H), 3.82 (ddd, $J$ = 9.2, 7.9 Hz, 1H), 4.07 (d, $J$ = 4.4 Hz, 1H), 4.18-4.27 (m, 4H), 4.37 (dd, $J$ = 9.2, 7.9 Hz, 1H), 4.69 (dd, $J$ = 9.7, 9.2 Hz, 1H), 9.10 (bs, 1H). Selected NOEs are between $\delta$ 3.82 (H-4) and $\delta$ 4.07 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 13.89 (q), 13.91 (q), 41.82 (d), 42.66 (d), 50.56 (d), 62.39 (t), 62.50 (t), 67.75 (t), 167.25 (s), 167.47 (s), 175.04 (s), 176.02 (s). Selected HMBC correlations are between $\delta$ 3.52 (H-3) and $\delta$ 176.02 (CO$_2$H), 42.66 (C-4), between $\delta$ 3.82 (H-4) and $\delta$ 50.56 (CH(CO$_2$Et)$_2$), 41.82 (C-3), between $\delta$ 4.37, 4.69 (H-5a,5b) and $\delta$ 176.02 (CO$_2$H), and between $\delta$ 4.07 (CH(CO$_2$Et)$_2$) and $\delta$ 41.82 (C-3), 42.66 (C-4); IR (neat) 3536, 2985, 1774, 1739, 1469, 1447, 1373, 1207, 1032 cm$^{-1}$; MS (EI) $m/z$ 288 (M$^+$, 8.9), 270 (13), 243 (100), 197 (94), 160 (91), 125 (70%); HRMS M$^+$ 288.0842 (calcd for C$_{12}$H$_{16}$O$_8$ 288.0845).
Methyl Trans-3-(di(ethoxycarbonyl)methyl)-2-oxotetrahydrofuran-4-carboxylate (14):

To a solution of 13 (200 mg, 0.69 mmol) in methanol (0.28 mL)–benzene (1.1 mL) was added (CH$_3$)$_3$SiCHN$_2$ (ca. 10% hexane solution, 1.5 mL) at room temperature. The mixture was stirred for 30 min at room temperature and concentrated. The residue was purified by column chromatography over silica gel with hexane–ether as eluent to give 14 (149 mg, 71%); $R_f = 0.4$ (hexane-ether = 1 : 1); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.28 (t, $J = 7.1$ Hz, 3H), 1.29 (t, $J = 7.1$ Hz, 3H), 3.53 (dd, $J = 9.5$ Hz, 4.4 Hz, 1H), 3.76 (s, 3H), 3.80 (ddd, $J = 9.7$, 9.5, 8.2 Hz, 1H), 4.05 (d, $J = 4.4$ Hz, 1H), 4.17–4.27 (m, 4H), 4.28 (dd, $J = 9.2$, 8.2 Hz, 1H), 4.65 (dd, $J = 9.7$, 9.2 Hz, 1H). Selected NOEs are between $\delta$ 3.80 (H-4) and $\delta$ 4.05 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 13.94 (q), 41.97 (d), 42.75 (d), 50.48 (d), 52.81 (q), 62.23 (t), 62.32 (t), 67.86 (t), 167.23 (s), 167.38 (s), 171.72 (s), 174.96 (s). Selected HMBC correlations are between $\delta$ 3.53 (H-3) and $\delta$ 171.72 (CO$_2$CH$_3$), 42.75 (C-4), between $\delta$ 3.80 (H-4) and $\delta$ 50.48 (CH(CO$_2$Et)$_2$), 41.97 (C-3), between $\delta$ 4.28, 4.65 (H-5a,5b) and $\delta$ 171.72 (CO$_2$CH$_3$), and between $\delta$ 4.05 (CH(CO$_2$Et)$_2$) and $\delta$ 41.97 (C-3), 42.75 (C-4); IR (neat) 2986, 1784, 1741, 1439, 1372, 1248, 1210, 1179, 1032 cm$^{-1}$; MS (EI) $m/z$ 302 (M$^+$, 7.5), 271 (17), 257 (64), 160 (100%); HRMS M$^+$ 302.1001 (calcd for C$_{13}$H$_{18}$O$_8$ 302.1002); Anal. Calcd for C$_{13}$H$_{18}$O$_8$: C, 51.65; H, 6.00. Found: C, 51.44; H, 5.88.
Preparation of 15a-b.

To a solution of 13 (144 mg, 0.5 mmol) in THF (0.7 mL) were added benzylamine (54 mg, 0.5 mmol), Et$_3$N (70 µL, 54 mg, 0.5 mmol), HOBT (1-hydroxybenzotriazole) (135 mg, 1 mmol) and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (100 mg, 0.52 mmol) at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH$_2$Cl$_2$. The organic phase was washed with saturated aqueous NaHCO$_3$ solution, 2M aqueous citric acid, saturated aqueous NaHCO$_3$ and water, dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ether (1 : 4) to give 15a (110 mg, 58%); R$_f$ = 0.3 (hexane-ether = 1 : 4); colorless needles; mp 119-121 °C (AcOEt-hexane); $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.24 (t, $J$ = 7.1 Hz, 3H), 1.25 (t, $J$ = 7.1 Hz, 3H), 3.51 (dd, $J$ = 8.7, 4.0 Hz, 1H), 3.61 (ddd, $J$ = 8.9, 8.7, 7.5 Hz, 1H), 4.00-4.21 (m, 5H), 4.42 (d, $J$ = 5.9 Hz, 2H), 4.45 (dd, $J$ = 8.8, 7.5 Hz, 1H), 4.52 (dd, $J$ = 8.9, 8.8 Hz, 1H), 6.48 (br, 1H), 7.26-7.35 (m, 5H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.94 (q), 42.64 (d), 44.10 (t), 44.14 (d), 50.35 (d), 62.38 (t), 68.88 (t), 127.74 (d), 127.89 (d), 128.81 (d), 137.65 (s), 167.54 (s), 168.28 (s), 170.14 (s), 175.52 (s). Selected HMBC correlations are between δ 3.51 (H-3) and δ 170.14 (CONH), 44.14 (C-4), between δ 3.61 (H-4) and δ 50.35 (CH(CO$_2$Et)$_2$), 42.64 (C-3), and between δ 4.45, 4.52 (H-5a,5b) and δ 170.14 (CONH).; IR (KBr) 3302, 2979, 1783, 1770, 1731, 1646, 1540, 1371, 1258, 1189, 1142, 1044, 1012, 701 cm$^{-1}$; MS
EI $m/z$ 377 (M$^+$, 15), 279 (28), 200 (67), 149 (77), 91 (100%); HRMS M$^+$ 377.1479 (calcd for C$_{19}$H$_{23}$NO$_7$ 377.1475).

15b: R$_f$ = 0.5 (hexane-ether = 1 : 4); colorless needles; mp 118-120 °C (benzene); $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 1.240 (t, $J$ = 7.1 Hz, 3H), 1.244 (t, $J$ = 7.1 Hz, 3H), 3.51 (dd, $J$ = 8.6, 4.0 Hz, 1H), 3.63 (ddd, $J$ = 8.9, 8.6, 7.6 Hz, 1H), 3.99-4.19 (m, 5H), 4.35 (dd, $J$ = 14.9, 5.8 Hz, 1H), 4.39 (dd, $J$ = 14.9, 6.0 Hz, 1H), 4.39 (dd, $J$ = 8.8, 7.6 Hz, 1H), 4.52 (dd, $J$ = 8.9, 8.8 Hz, 1H), 6.73 (broad t, $J$ = 5.8 Hz, 1H), 7.20-7.23 (m, 2H), 7.27-7.31 (m, 2H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 13.89 (q), 42.48 (d), 43.27 (t), 44.09 (d), 50.31 (d), 62.36 (t), 62.39 (t), 68.85 (t), 128.83 (d), 129.23 (d), 133.43 (s), 136.33 (s), 167.53 (s), 168.22 (s), 170.24 (s), 175.62 (s). Selected HMBC correlations are between $\delta$ 3.51 (H-3) and $\delta$ 170.24 (CONH), 44.09 (C-4), between $\delta$ 3.63 (H-4) and $\delta$ 50.31 (CH(CO$_2$Et)$_2$), 42.48 (C-3), and between $\delta$ 4.39, 4.52 (H-5a,5b) and $\delta$ 170.24 (CONH).; IR (KBr) 3291, 2979, 1784, 1771, 1744, 1645, 1541, 1370, 1261, 1189, 1016 cm$^{-1}$; MS (EI) $m/z$ 413 (M$^+$, 4.3), 411 (M$^+$, 13), 366 (13), 243 (44), 140 (100%); HRMS M$^+$ 411.1084, 413.1062 (calcd for C$_{19}$H$_{22}$ClNO$_7$ 411.1085, 413.1055); Anal. Calcd for C$_{19}$H$_{22}$ClNO$_7$: C, 55.41; H, 5.38; N, 3.40. Found: C, 55.26; H, 5.15; N, 3.32.
Preparation of 16a (eq. 3-4).

To a mixture of phenylboronic acid (39 mg, 0.323 mmol), 12c (155 mg, 0.307 mmol), K$_2$CO$_3$ (106 mg, 0.769 mmol) were added acetone (0.61 ml), water (0.77 mL), and Pd(OAc)$_2$ (4.0 mmol/L acetone solution, 0.31 mL, 1.24 μmol), successively. The mixture was heated at 65 °C for 18 h. The reaction mixture was extracted with dichloromethane (4 × 20 mL) and the organic phase was washed with brine, dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ether to give 16a (78 mg, 58%); R$_f$ = 0.6 (hexane-ether = 1 : 4); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.19 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 3.00 (dd, J = 9.6, 7.6 Hz, 1H), 3.40 (dd, J = 9.2, 5.1 Hz, 1H), 3.48 (dd, J = 9.6, 9.2 Hz, 1H), 3.77 (dddd, J = 9.2, 9.2, 7.6, 0.9 Hz, 1H), 3.96 (d, J = 5.1 Hz, 1H), 4.07-4.25 (m, 4H), 4.40 (d, J = 14.8 Hz, 1H), 4.51 (d, J = 14.8 Hz, 1H), 5.13 (d, J = 0.9 Hz, 1H), 5.27 (s, 1H), 7.22-7.33 (m, 10H). Selected NOEs are between δ 3.40 (H-3) and δ 5.13 (=CHH) and between δ 3.77 (H-4) and δ 3.96 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.97 (q), 14.02 (q), 39.38 (d), 45.71 (d), 46.82 (t), 51.01 (d), 51.75 (t), 61.65 (t×2), 113.10 (t), 126.74 (d), 127.63 (d), 127.93 (d), 128.14 (d), 128.54 (d), 128.71 (d), 136.04 (s), 140.62 (s), 148.69 (s), 168.08 (s), 168.23 (s), 172.77 (s). Selected HMBC correlations are between δ 3.40 (H-3) and δ 51.01 (CH(CO$_2$Et)$_2$), 39.38 (C-4), between δ 3.77 (H-4) and δ 51.01 (CH(CO$_2$Et)$_2$), 45.71 (C-3), between δ 3.00, 3.48 (H-5a,5b) and δ 148.69 (CPh=CH$_2$), and between δ 3.96 (CH(CO$_2$Et)$_2$) and δ 45.71 (C-3), 39.38 (C-4); IR (neat) 2982, 2936,
1732, 1695, 1495, 1444, 1370, 1261, 1176, 1030 cm$^{-1}$; MS (EI) $m/z$ 435 (M$^+$, 5), 276 (11), 220 (26), 205 (100%); HRMS M$^+$ 435.2042 (calcd for C$_{26}$H$_{29}$NO$_5$ 435.2046).

**16b**: $R_f = 0.4$ (hexane-ether = 1 : 4); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (ppm) 0.877 (t, $J = 7.4$ Hz, 3H), 1.19 (t, $J = 7.1$ Hz, 3H), 1.24 (t, $J = 7.1$ Hz, 3H), 1.51 (qt, $J = 7.4, 7.4$ Hz, 2H), 3.10 (dd, $J = 9.3, 7.4$ Hz, 1H), 3.23 (t-like, $J = 7.4$ Hz, 2H), 3.36 (dd, $J = 9.1, 5.3$ Hz, 1H), 3.59 (dd, $J = 9.3, 9.2$ Hz, 1H), 3.79 (dd and, $J = 9.2, 9.1, 7.4, 0.9$ Hz, 1H), 3.92 (d, $J = 5.3$ Hz, 1H), 4.06-4.24 (m, 4H), 5.16 (d, $J = 0.9$ Hz, 1H), 5.30 (s, 1H), 7.28-7.35 (m, 5H). Selected NOEs are between $\delta$ 3.36 (H-3) and $\delta$ 5.16 ($=CHH$), 7.28-7.35 (Ph), and between $\delta$ 3.79 (H-4) and $\delta$ 3.92 ($CH(CO$_2$Et)$_2$). $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 11.24 (q), 13.96 (q), 14.00 (q), 20.39 (t), 39.37 (d), 44.46 (t), 45.86 (d), 51.09 (d), 52.32 (t), 61.56 (t), 61.60 (t), 112.85 (t), 126.75 (d), 127.95 (d), 128.57 (d), 140.79 (s), 149.01 (s), 168.09 (s), 168.32 (s), 172.57 (s). Selected HMBC correlations are between $\delta$ 3.36 (H-3) and $\delta$ 51.09 ($CH(CO$_2$Et)$_2$), 39.37 (C-4), between $\delta$ 3.79 (H-4) and $\delta$ 51.09 ($CH(CO$_2$Et)$_2$), 45.85 (C-3), and between $\delta$ 3.92 ($CH(CO$_2$Et)$_2$) and $\delta$ 45.85 (C-3), 39.37 (C-4). IR (neat) 2965, 2934, 1732, 1695, 1493, 1444, 1370, 1264, 1177, 1148, 1033 cm$^{-1}$; MS (EI) $m/z$ 387 (M$^+$, 16), 342 (9.3), 228 (100%); HRMS M$^+$ 387.2036 (calcd for C$_{22}$H$_{29}$NO$_5$ 387.2046).
3-5 References


Chapter 4

Cyclization Reactions of Substituted Allenyl Ethenetricarboxylates

4-1 Introduction

Oxygen and nitrogen-containing six-membered heterocyclic compounds such as dihydro and tetrahydropyrans and piperidines, are common structural units in biologically active compounds.\textsuperscript{1,2} The development of new efficient synthetic strategies for the construction of this type of heterocycles is of considerable importance from the viewpoint of the medicinal and organic chemistry.

Yamazaki and coworkers have developed Lewis acid-promoted 3,4-\textit{trans} stereoselective five-membered ring formation of alkenyl ethenetricarboxylates (eq. 4-1).\textsuperscript{3}

\[
\begin{align*}
\text{EtO}_2\text{C}-\text{C}=\text{CO}_2\text{Et} & \xrightarrow{1) \text{MX}_n} \text{EtO}_2\text{C}-\text{C}=\text{CO}_2\text{Et} \\
\text{Y} & \quad \text{X} = \text{Cl, Br, I} \\
\text{2) H}_2\text{O} & \quad \text{MX}_n = \text{TiCl}_4, \text{TiBr}_4, \\
& \quad \text{AlCl}_3, \text{AlBr}_3, \text{FeCl}_3, \text{ZnI}_2
\end{align*}
\]

(4-1)

In the course of the research on Lewis acid-promoted cyclization reaction of alkenyl esters, the six-membered ring formation from 2-methyl-2-propenyl ester of ethenetricarboxylate was found (eq. 4-2).

\[
\begin{align*}
\text{EtO}_2\text{C}-\text{C}=\text{CO}_2\text{Et} & \xrightarrow{1) \text{AlCl}_3, \text{r.t. 3 h}} \text{EtO}_2\text{C}-\text{C}=\text{CO}_2\text{Et} \\
\text{1} & \quad \text{H} \\
\text{CH}_2\text{Cl}_2 & \quad \text{2) H}_2\text{O} \\
& \quad \text{Cl} (70%)
\end{align*}
\]

(4-2)
In order to extend the scope of the six-membered ring formation and gain an insight into the mechanism for the selectivity, Lewis acid-promoted reaction of the corresponding allene derivative has been examined in this study.

4-2 Results and Discussion

Mitsunobu conditions of 1,1-diethyl 2-hydrogen ethenetricaboxylate and 2-methylbuta-2,3-dienol (PPh$_3$ and DEAD (diethyl azodicarboxylate) in ether) gave 2-methylbuta-2,3-dienyl ethenetricarboxylate 3 in low yield. Therefore, substrate 3 was prepared by the Wittig reaction of diethyl ketomalonate with the corresponding (triphenylphosphoranylidne)acetate (eq. 4-3).

\[
\text{EtO}_2\text{C CO}_2\text{Et} + \text{EtO}_2\text{C CO}_2\text{Et} \rightarrow \text{EtO}_2\text{C CO}_2\text{Et} + \text{EtO}_2\text{C CO}_2\text{Et} \quad (4-3)
\]

The reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate 3 with one equivalent of various Lewis acids such as AlCl$_3$, SnCl$_4$, EtAlCl$_2$, TiCl$_4$, and FeCl$_3$ in CH$_2$Cl$_2$ at room temperature gave 4-(chloromethyl)-3,6-dihydro-5-methyl-2-oxo-2$H$-pyran 4 as a major product (Table 4-1). The $\delta$-lactone structure of 4 was suggested by the observed C=O absorptions (1738 cm$^{-1}$ together with ethyl esters). $^1$H, $^{13}$C, and 2D NMR spectra were in agreement with the six-membered ring structure.
A small amount of \( t\)-4-(2-chlorovinyl)-c-4-methyl-2-oxotetrahydrofuran 5 was formed in entries 1-4.

Use of TiCl\(_4\) gave compound 4 (46%) and 5 (30%).

**Table 4-1.** Reactions of 2-methylbuta-2,3-dienyl ethenetricarboxylate 3

<table>
<thead>
<tr>
<th>Entry</th>
<th>MX(_n)</th>
<th>4 Yield (%)</th>
<th>5 Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AlCl(_3)</td>
<td>56</td>
<td>a</td>
</tr>
<tr>
<td>2</td>
<td>SnCl(_4)</td>
<td>64</td>
<td>a</td>
</tr>
<tr>
<td>3</td>
<td>EtAlCl(_2)</td>
<td>38</td>
<td>a</td>
</tr>
<tr>
<td>4</td>
<td>TiCl(_4)</td>
<td>46</td>
<td>30</td>
</tr>
<tr>
<td>5</td>
<td>FeCl(_3)</td>
<td>32</td>
<td>a</td>
</tr>
</tbody>
</table>

\( ^a \) A small amount of 5 was detected by \(^1\)H NMR but could not be isolated.

The \( \gamma \)-lactone structure of 5 was suggested by the presence of a characteristic C=O absorption (1789 cm\(^{-1}\)). \(^1\)H, \(^13\)C, and 2D NMR spectra were in agreement with the five-membered ring structure. The 3,4-stereochemistry of 2-oxotetrahydrofuran 5 was examined by NOESY experiments. NOEs between 4-Me and \( CH(CO_2Et)_2 \) were observed. Thus, the 3,4-stereochemistry of 5 concerning \( CH(CO_2Et)_2 \) and CX=CH\(_2\) groups is the same as the cyclized products in Chapter 3.

The possible reaction mechanism for formation of the major product 4, the minor product 5 and an undetected six-membered compound 6 is shown in Scheme 4-1. Direct six-membered ring formation (route a) may lead to intermediate B. Protonation and removal of AlCl\(_2\)OH yield the major product 4. Other possible routes and intermediates C, D, and E are also depicted, which could be
considered following the reactions in eq. 4-2 and in Chapter 3. The six-membered ring formation (route a) may occur preferably, since 1,1-dialkylallenes described in Chapter 2 reacted at the central carbon of allene moiety intermolecularly.

Scheme 4-1. Possible reaction mechanism for cyclization of allyl ester 3 to 2-oxodihydropyran 4, 6, and 2-oxotetrahydrofuran 5.
4-3 Conclusion

In summary, a Lewis acid-promoted reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate 3 to give 4-(chloromethyl)-3,6-dihydro-5-methyl-2-oxo-2\(H\)-pyran 4 has been found. The preference for six- over five-membered ring formation has been observed. The oxygen-containing six-membered heterocycle generated in this reaction should be a versatile synthetic intermediate. Further study on the related Lewis acid-promoted six-membered ring formation will disclose the detailed reaction mechanism and extend the synthetic utility.

4-4 Experimental Section

General Procedures

IR spectra were recorded in the FT-mode on a JASCO FT/IR-460 Plus spectrophotometer. \(^1\)H NMR spectra were recorded at 400 MHz and \(^{13}\)C NMR spectra were recorded at 100.6 MHz on a Varian INOVA-400 spectrometer. \(^1\)H chemical shifts are reported in ppm relative to Me\(_4\)Si and \(^{13}\)C chemical shifts are reported in ppm relative to CDCl\(_3\) (77.1 ppm). \(^{13}\)C mutiplicities were determined by DEPT and HSQC. Peak assignments are made by 2D COSY, HSQC, NOESY, and HMBC spectra. Mass spectra were recorded by EI techniques on a JEOL JMS-700 mass spectrometer.
2-Methylbuta-2,3-dienyl ethenetricarboxylate 3 was prepared by the Wittig reaction of diethyl ketomalonate with the corresponding (triphenylphosphoranylidene)acetate according to the literature procedure. The (triphenylphosphoranylidene)acetate ester was prepared by the reaction of the corresponding chloroacetate with triphenylphosphine in benzene and subsequent treatment with NaOH. The chloroacetate was prepared by the reaction of 2-methylbuta-2,3-dienol (1 equivalent) with chloroacetyl chloride (1 equivalent) in the presence of pyridine (1 equivalent) in ether at 0 °C.

1,1-Diethyl 2-methylbuta-2,3-dienyl ethenetricarboxylate (3): Rf = 0.6 (hexane-ether = 1 : 1); pale yellow oil; 1H NMR (400 MHz, CDCl3) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 1.73 (t, J = 3.2 Hz, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 4.64 (t, J = 2.3 Hz, 2H), 4.76 (qt, J = 3.2, 2.3 Hz, 2H), 6.89 (s, 1H); 13C NMR (100.6 MHz, CDCl3) δ (ppm) 13.94 (q), 14.00 (q), 15.78 (q), 62.15 (t), 62.57 (t), 67.17 (t), 75.86 (t), 94.06 (s), 129.72 (d), 139.27 (s), 162.29 (s), 163.36 (s), 164.22 (s), 207.40 (s); IR (neat) 2985, 1963, 1728, 1652, 1446, 1374, 1344, 1259, 1177, 1067, 1022 cm⁻¹; MS (El) m/z 282 (M⁺); HRMS M⁺ 282.1101 (calcd for C14H16O6 282.1103).

Diethyl 4-(Chloromethyl)-5-methyl-2-oxo-2H-3,6-dihydropyran-3-yl)malonate (4): Typical Experimental Procedure (Table 4-1, entry 2).

To a solution of 3 (141 mg, 0.5 mmol) in CH2Cl2 (2 mL) was added SnCl₄ (60 µL, 130 mg, 0.5 mmol).
The mixture was stirred at room temperature for 18 h. The reaction mixture was poured into saturated aqueous NaHCO$_3$ solution. The mixture was extracted with dichloromethane and the organic phase was dried (Na$_2$SO$_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ether to give 4 (98 mg, 64%); R$_f$ = 0.3 (hexane-ether = 1 : 2); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) δ (ppm) 1.27 (t, $J$ = 7.1 Hz, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H), 1.81 (s, 3H), 3.89 (bs, 1H), 4.00 (d, $J$ = 3.5 Hz, 1H), 4.08 (d, $J$ = 12.1 Hz, 1H), 4.14-4.33 (m, 5H), 4.64 (bd, $J$ = 16.7 Hz, 1H), 4.95 (bd, $J$ = 16.7 Hz, 1H). Selected NOEs are between δ 4.00 (CH(CO$_2$Et)$_2$) and δ 3.89 (H-3), 4.08, 4.14-4.33 (CH$_2$Cl), between δ 1.81 (5-CH$_3$) and δ 4.08, 4.14-4.33 (CH$_2$Cl), 4.64, 4.95 (H-6a,6b).; $^{13}$C NMR (100.6 MHz, CDCl$_3$) δ (ppm) 13.97 (q), 14.02 (q), 14.41 (q), 40.82 (t), 41.66 (d), 52.55 (d), 61.92 (t), 62.27 (t), 71.44 (t), 122.69 (s), 133.64 (s), 167.59 (s), 167.64 (s), 168.74 (s). Selected HMBC correlations are between δ 3.89 (H-3) and δ 168.74 (C-2), between δ 4.64, 4.95 (H-6a,6b) and δ 122.69 (C-4), 133.64 (C-5), between δ 4.08, 4.14-4.33 (CH$_2$Cl) and δ 122.69 (C-4), 133.64 (C-5), and between δ 1.81 (5-CH$_3$) and δ 122.69 (C-4), 133.64 (C-5), 71.44 (C-6).; IR (neat) 2983, 1738, 1454, 1373, 1338, 1292, 1262, 1206, 1176, 1159, 1084, 1055, 1031 cm$^{-1}$; MS (EI) m/z 320 (M$^+$, 0.6), 318 (M$^+$, 1.3), 273 (3.8), 159 (24), 91 (44), 84 (100%); HRMS M$^+$ 318.0866, 320.0862 (calcd for C$_{14}$H$_{10}$ClO$_6$ 318.0870, 320.0841).
Diethyl 2-[Trans-4-(1-chlorovinyl)-cis-4-methyl-2-oxotetrahydrofuran-3-yl]malonate (5):

(including a small amount of impurity); R_f = 0.6 (hexane-ether = 1 : 2); pale yellow oil; ^1H NMR (400 MHz, CDCl_3) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.43 (s, 3H), 3.50 (d, J = 11.0 Hz, 1H), 3.88 (d, J = 9.0 Hz, 1H), 4.01-4.09 (m, 2H), 4.13-4.21 (m, 1H), 4.24-4.32 (m, 2H), 4.52 (dd, J = 9.0, 0.8 Hz, 1H), 5.41 (d, J = 2.4 Hz, 1H), 5.47 (d, J = 2.4 Hz, 1H). Selected NOEs are between δ 1.43 (4-CH_3) and δ 3.50 (CH(CO_2Et)_2), 3.88 (H-5a), 5.41 (=CHH); ^13C NMR (100.6 MHz, CDCl_3) δ (ppm) 13.84 (q), 13.99 (q), 18.59 (q), 46.00 (d), 49.63 (d), 49.72 (s), 61.99 (t), 62.23 (t), 74.92 (t), 116.63 (t), 142.28 (s), 166.03 (s), 166.58 (s), 174.23 (s). Selected HMBC correlations are between δ 1.43 (4-CH_3) and δ 46.00 (C-3), 49.72 (C-4), 74.92 (C-5), 142.28 (CCl=), between δ 3.88 (H-5a) and δ 46.00 (C-3), 49.72 (C-4), 74.23 (C-2), between δ 3.88, 4.52 (H-5a,5b) and δ 142.28 (CCl=), 18.59 (4-CH_3), and between δ 5.41, 5.47 (=CH_2) and δ 142.28 (CCl=), 49.72 (C-4); IR (neat) 2983, 1789, 1763-1733, 1627, 1466, 1393, 1368, 1275, 1137, 1028 cm^{-1}.

4-5 References

Nat. Prod. 2011, 74, 2582.


Chapter 5

Conclusion

In this research, the author has studied on Lewis Acid-promoted cyclization reactions utilizing allenes to lead to a series of synthetically useful heterocyclic and carbocyclic compounds.

In chapter 2, the author has investigated Lewis acid-promoted addition/cyclization reaction of 1,1-diarylallenes with α,β-unsaturated carbonyl compounds. The reaction of arylallenes and ethenetricarboxylate derivatives with Lewis acids gave indene derivatives efficiently, via a conjugate addition/cyclization reaction. The Lewis acid-catalyzed reaction of alkylallene with ethynetricarboxylate derivatives gave the γ-lactone. The author applied the reaction of arylallenes to other electrophiles. SnCl$_4$-promoted reaction of diarylallenes and vinyl ketones gave indene derivatives. The reaction of diphenylallene with diethyl ketomalonate in the presence of SnCl$_4$ at -40 °C gave hydroxyindenylmalonate as a major product via carbonyl addition/cyclization reaction. The reaction at 80 °C gave indenylmalonate.

In chapter 3, the author has developed Lewis acid-promoted cyclization reactions of allenyl ethenetricarboxylates and the amides. Reaction of allenyl ethenetricarboxylates and the amides with Lewis acids such as AlCl$_3$, AlBr$_3$, and ZnX$_2$ (X = Cl, Br, I) gave 3,4-$trans$ haloalkenyl five-membered heterocycles stereoselectively. The stereochemistry was determined by NOE experiments and
reduction of the cyclized products. Various transformations of the haloalkenyl functionalized cyclic compounds have also been demonstrated.

In chapter 4, the author has examined the cyclization reactions of substituted allenyl ethenetricarboxylates. The reaction of 2-methylbuta-2,3-dienyl ethenetricarboxylate with Lewis acids such as AlCl₃ and SnCl₄ gave a chlorine-incorporated six-membered oxygen-containing heterocycle preferentially. The selectivity of the ring closure for six- over five-membered rings is noteworthy.

In this thesis, the usefulness of the Lewis acid-promoted cyclization reactions of allenes in organic synthesis has been established. On the basis of this methodology, highly functionalized heterocyclic and carbocyclic compounds were synthesized. The knowledge gained in this study is expected to be useful in developing new materials and medical supplies.
List of Publications

1. Lewis Acid Promoted Reactions of Ethenetricarboxylates with Allenes: Synthesis of Indenes and γ-Lactones via Conjugate Addition/Cyclization Reaction
S. Yamazaki, Y. Yamamoto, Y. Fukushima, M. Takebayashi, T. Ukai, Y. Mikata

2. Lewis Acid Promoted Reactions of 1,1-Diarylallenes and Ketone Derivatives: Synthesis of Indenes by an Addition/Cyclization Reaction
S. Yamazaki, Y. Fukushima, T. Ukai, K. Tatsumi, A. Ogawa

3. Lewis Acid-Promoted Cyclization/Halogenation of Allenyl Ethenetricarboxylates and the Amides: Stereoselective Synthesis of Haloalkenyl Five-Membered Heterocycles
Y. Fukushima, S. Yamazaki, A. Ogawa

4. Six-Membered Ring Formation from Lewis Acid-Promoted Reaction of 2-Methyl-2-alkenyl Amides and Esters of Ethenetricarboxylate
S. Yamazaki, K. Ueda, Y. Fukushima, A. Ogawa, K. Kakiuchi
Other Publication

1. Efficient Synthesis of Heterocyclic Compounds Using Ethenetricarboxylic Acid Diesters
S. Yamazaki, Y. Iwata, Y. Fukushima

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Yugo Fukushima