This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the Information for Authors.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal’s standard Terms & Conditions and the Ethical guidelines still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.
Lewis Acid-Promoted Cyclization/Halogenation of Allenyl Ethenetricarboxylates and the Amides: Stereoselective Synthesis of Haloalkenyl Five-membered Heterocycles

Yugo Fukushima, a Shoko Yamazaki,* a and Akiya Ogawa b

aDepartment of Chemistry, Nara University of Education, Takabatake-cho, Nara 630-8528, Japan, bDepartment of Applied Chemistry, Graduate School of Engineering, Osaka Prefecture University, Gakuen-cho 1-1, Nakaku, Sakai, Osaka 599-8531, Japan

Abstract: Lewis acid-promoted intramolecular reactions of allenyl ethenetricarboxylates and the corresponding amides have been examined. 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 performed.

Introduction

Development of new synthetic reactions utilizing allenes has attracted attention due to their structural features. 1 Transition metal catalyzed cyclization 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. 2
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 actetals 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. We 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 1).

\[
\begin{align*}
\text{EtO}_2\text{C} & \text{CO}_2\text{Et} \\
\text{Y} & = \text{O}, \text{NR} \\
\end{align*}
\]

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

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 2).
The reaction of allenyl ethenetricarboxylates 3a,b with 1 equivalent of various Lewis acid such as AlCl₃, AlBr₃, SnCl₄, TiCl₄, FeCl₃, InCl₃, or InBr₃ in CH₂Cl₂ at room temperature gave 3,4-trans haloalkenyl tetrahydrofuran derivatives 4a-d stereoselectively (eq 3, Table 1). Among these 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 1. Reactions of Allenyl Esters 3a,b

<table>
<thead>
<tr>
<th>Entry</th>
<th>3</th>
<th>R</th>
<th>MXₙ</th>
<th>Time (h)</th>
<th>4</th>
<th>X</th>
<th>Yield (%)</th>
<th>Byproduct (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>H</td>
<td>AlCl₃</td>
<td>18</td>
<td>4a</td>
<td>Cl</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3a</td>
<td>H</td>
<td>AlBr₃</td>
<td>18</td>
<td>4b</td>
<td>Br</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>H</td>
<td>SnCl₄</td>
<td>3</td>
<td>4a</td>
<td>Cl</td>
<td>42</td>
<td>5 (ca. 19)²</td>
</tr>
<tr>
<td></td>
<td>3a</td>
<td>H</td>
<td>TiCl₄</td>
<td>3</td>
<td>4a</td>
<td>Cl</td>
<td>5</td>
<td>(ca. 18)a</td>
</tr>
<tr>
<td>---</td>
<td>----</td>
<td>-----</td>
<td>-------</td>
<td>----</td>
<td>-----</td>
<td>------</td>
<td>-------</td>
<td>-----------</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>H</td>
<td>TiBr₄</td>
<td>18</td>
<td>4b</td>
<td>Br</td>
<td>6</td>
<td>(30)</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>H</td>
<td>FeCl₃</td>
<td>3</td>
<td>4a</td>
<td>Cl</td>
<td>6</td>
<td>(54)b</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>H</td>
<td>InCl₃</td>
<td>18</td>
<td>4a</td>
<td>Cl</td>
<td>6</td>
<td>(20), 3a (44%)</td>
</tr>
<tr>
<td>8</td>
<td>3b</td>
<td>Me</td>
<td>AlCl₃</td>
<td>18</td>
<td>4c</td>
<td>Cl</td>
<td>6</td>
<td>(36)</td>
</tr>
<tr>
<td>9</td>
<td>3b</td>
<td>Me</td>
<td>SnCl₄</td>
<td>18</td>
<td>4c</td>
<td>Cl</td>
<td>6</td>
<td>(16)</td>
</tr>
</tbody>
</table>

a Small amounts of impurity could not be removed.  
b The yields were estimated by the NMR spectra of the mixture of 4a and 6.  
c 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⁻¹) and disappearance of the 1958-1972 cm⁻¹ absorption for C=C=CH allene moiety in 3a,b. ¹H, ¹³C 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-cis and trans diastereomers. The following peaks were used for the assignment of haloalkenyl 2-oxotetrahydrofurans 4a-d. NOEs between H-3 and CH=CH₂ (X = Cl, Br) for 4a,b and between H-4 and CH(CO₂Et)₂ for 4a-d were observed. Thus, the 3,4-trans stereochemistry of 4a-d was likely, similar to cyclic products in eq 1. On the other hand, NOESY spectra of by-product 4-ethylnitetrahydrofuran 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-ethylnitetrahydrofuran 5, the following transformations have been carried out. Hydrogenolysis of the 4-chlorovinyl-2-oxotetrahydrofuran 4a gave 3,4-trans-4-ethyl-2-oxotetrahydrofuran 7t in 51% yield (Scheme 1). Hydrogenolysis of both carbon-chlorine bond and carbon-carbon double bond occurred. ¹⁶ 3,4-Trans-4-(1-chloroethyl)-2-oxotetrahydrofuran 8 is obtained by the Lewis acid promoted reaction of alkenyl ester 9 stereoselectively.¹¹ Dechlorination of compound 8 did not proceed under the conditions used for 4a. The reaction of 8 with Bu₃SnH and AIBN gave a dechlorinated tetrahydrofuran in 89% yield. This was identical to 7t obtained from 4a. Thus, the
Stereochemistry of 7t was assigned as 3,4-trans. The stereochemistry of 7t was also determined by NOESY experiment. Next, hydrogenolysis of ethynyl group of 5 was conducted. The hydrogenated product 7c is different from 7t and could be assigned as 3,4-cis-4-ethyl-2-oxotetrahydrofuran. Therefore, the stereochemistry of 5 is determined as 3,4-cis.

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

The Lewis acid-promoted reaction of 2-penta-3,4-dienyl ester 3c (shown in eq 2) was also examined. However, the reaction of 3c with 1 equivalent of AlCl₃, AlBr₃, and SnCl₄ gave complex mixtures. Six-membered ring formation was not an efficient process.

![Equation 4](image)
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 Et₃N (eq 4). Reaction of diethyl 2-((N-allenyl-N-benzylcarbamoyl)methylene)malonate (11a) with AlCl₃, ZnCl₂, ZnBr₂, and ZnI₂ at room temperature gave 3,4-trans-4-(1-chloro(or bromo/iodo)vinyl)-2-oxopyrrolidines 12a-c in 55-76% yields (eq 5, Table 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 AlBr₃ also gave 12b,e but lower yields than those of ZnBr₂ (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). ¹H, ¹³C and 2D NMR spectra were in agreement with the five-membered ring structure. The 3,4-trans stereochemistry was determined by NOEs. NOEs between H-3 and CX=CHH (X = Cl, Br, I)¹⁵ and between H-4 and CH(C₂O₂Et)₂ were observed.

![Chemical structure of 11a and 11b]

Table 2. Reactions of Allenyl Amides 11

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>MXₙ</th>
<th>(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>
<td>55</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Ph</td>
<td>ZnCl₂</td>
<td>1×2</td>
<td>Cl</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>CH₂Ph</td>
<td>ZnBr₂</td>
<td>1×2</td>
<td>Br</td>
<td>64</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Ph</td>
<td>ZnI₂</td>
<td>2</td>
<td>I</td>
<td>58</td>
</tr>
<tr>
<td>5</td>
<td>CH₂CH₂CH₃</td>
<td>AlCl₃</td>
<td>1</td>
<td>Cl</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>CH₂CH₂CH₃</td>
<td>ZnBr₂</td>
<td>1×2</td>
<td>Br</td>
<td>64</td>
</tr>
<tr>
<td>7</td>
<td>CH₂CH₂CH₃</td>
<td>ZnI₂</td>
<td>1×2</td>
<td>I</td>
<td>68</td>
</tr>
</tbody>
</table>
The reaction with ZnX₂ (1 equiv) 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 equiv) to give the products 12.

In order to demonstrate the utility of the cyclization reaction, synthetic transformations of the products were examined. 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 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 experiment. Derivatization of 13 with benzylamines 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 proceeds smoothly to give phenyl-substituted pyrrolidines (16a,b) (eq 6).

![Scheme 2. Transformation of 4a](image-url)
The reaction mechanism to give the halogenated five-membered heterocycles with 3,4-\textit{trans} stereochemistry is proposed similar to that for the reaction of the allyl ester of ethenetetracarboxylates (eq 1)\textsuperscript{11} and shown in Scheme 3. \textit{Trans} precursor A\textsubscript{1} and \textit{cis} precursor A\textsubscript{2} in Scheme 4 may be formed from 3 and Al\textsubscript{2}Cl\textsubscript{6} reversibly. The reaction may start from the precursor A\textsubscript{1} consisting of 3 and Al\textsubscript{2}Cl\textsubscript{6}. The C-C bond formation and Cl-C bond formation from A\textsubscript{1} may occur concertedly to lead to cyclized intermediate B\textsubscript{1}. Intermolecular Cl\textsuperscript{-} anti attack leading to 3,4-\textit{trans} cyclized product can be explained by steric reason. One molecule of Lewis acid (AlCl\textsubscript{3}) may work as a catalyst and could be released after the cyclization step. Protonation and removal of AlCl\textsubscript{2}(OH) yield the product 4.

In order to support the proposed mechanism, the structures of the intermediates and transition states of model compounds (the corresponding methyl esters and Al\textsubscript{2}Cl\textsubscript{6}) were calculated using B3LYP/6-31G\textsuperscript{*}.\textsuperscript{17,18} TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has single imaginary frequencies (v\textsuperscript{±}). From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC) method\textsuperscript{19} to obtain the energy-minimum geometries. Relative Gibbs free energies were refined by single-point calculations of RB3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH\textsubscript{2}Cl\textsubscript{2})\textsuperscript{20} on the RB3LYP/6-31G\textsuperscript{*} geometries and their thermal corrections (T = 298.15 K, P = 1 atm). \(\Delta G^\ddagger\) for TS1 leading to 3,4-\textit{trans} tetrahydrofuran is found to be lower than that of TS2 leading to 3,4-\textit{cis} tetrahydrofuran (Schemes 3,4). Two conformational isomers, \textit{trans} precursor A\textsubscript{1} and \textit{cis} precursor A\textsubscript{2} were obtained. A\textsubscript{2} is 5.15 [1.28] kcal/mol more stable than A\textsubscript{1}. The energy difference may be small enough and they are considered to exist as interconverting forms. Although the barrier for conformational change has not been computed, the Curtin-Hammett principle\textsuperscript{21} may be applicable in this case. The calculation results are similar to those for allyl
ester + Al₂Cl₆.¹¹ Thus, formation of 3,4-trans five-membered rings are lower energy process than that of 3,4-cis. The results support the assignment of 3,4-trans stereochemistry for the products 4.

Calculations of 1:1 complex of the substrate and AlCl₃ were also examined (Supplementary Information). Although the concerted formations of both 3,4-cis and trans tetrahydrofuran rings by intramolecular Cl⁻ attack were calculated, they have higher activation energies (ΔG‡) than the systems of the substrate and Al₂Cl₆. In addition, the AlCl₃-promoted concerted process to form by-product, 3,4-cis-4-ethynyltetrahydrofuran 5 (Table 1, entries 3-5) as a model system for Scheme 5 was obtained. The activation energy (ΔG‡) for formation of 5 with AlCl₃ is also higher than the systems of the substrate and Al₂Cl₆. Further mechanistic studies are underway.
Scheme 3. Proposed reaction mechanism for cyclization of allyl ester model compound 3m (R = Me) with Al₂Cl₆. Relative Gibbs free energies (T = 298.15 K and P = 1 atm) for intermediates and TSs (transition states) of the model compounds (3m + Al₂Cl₆) are obtained by B3LYP/6-31G* (without brackets) and [B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH₂Cl₂) // B3LYP/6-31G*] (with square brackets [  ]).

Scheme 4. The reaction pathway leading to 3,4-čís 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.
Scheme 5. Formation of by-product 5

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 Scheme 6. Ester 3 is 8.98 [7.67] kcal/mol more stable in s-cis conformation, probably because of the steric repulsion. On the other hand, the energy difference of s-cis and s-trans conformations of amide 11 is small. In order to cyclize, they must have s-trans conformations. The different reactivities of esters and amides may arise from their structural features.
Scheme 6. The model compounds, dimethyl esters with allenyl group 3m and 11m optimized by B3LYP/6-31G* and their relative energies $\Delta G^\circ$. $\Delta G^\circ$ is the difference of Gibbs free energies ($T = 298.15$ K, $P = 1$ atom) of B3LYP/6-31G* (without brackets) and [B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH$_2$Cl$_2$) // B3LYP/6-31G*] (with square brackets [ ]), relative to that of s-cis conformations.

In summary, a Lewis acid-promoted reaction of allenyl ethenetricarboxylates 3a,b and the amides 11a,b to give haloalkenyl oxygen and nitrogen-containing five-membered heterocycles has been found. The reaction gave 3,4-trans substituted cyclized products stereoselectively. AlCl$_3$ and AlBr$_3$ gave 2-oxotetrahydrofurans, and AlCl$_3$, ZnX$_2$ (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.
Experimental Section

**General Methods.** $^1$H Chemical shifts are reported in ppm relative to Me$_4$Si. $^{13}$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.

Allenyl alcohols 2a,b,c were prepared according to the literature.$^{5a,22,23}$

**1,1-Diethyl 2-buta-2,3-dienyl ethene-1,1,2-tricarboxylate (3a)** To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (432 mg, 2 mmol) (prepared from 1,1-diethyl 2-tert-butyl ethenetricarboxylate (545 mg, 2 mmol) upon treatment with CF$_3$CO$_2$H) in ether (2 mL) were added diethyl azodicarboxylate 40% in toluene (0.91 mL, 2 mmol), PPh$_3$ (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%).

3a: $R_f = 0.8$ (ether); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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), 4.33 (q, $J = 7.1$ Hz, 2H), 4.49 (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), 5.70 (s, 1H); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (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$^{-1}$; MS (EI) m/z 269 (M$^+$, 29), 200 (90), 199 (93), 143 (100%); HRMS M$^+$ 268.0945 (calcd for C$_{13}$H$_{16}$O$_6$ 268.0947); Anal. Calcd for C$_{13}$H$_{16}$O$_6$: C, 58.20; H, 6.01. Found: C, 58.05; H, 5.81.

3b: $R_f = 0.8$ (ether); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (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+1)$^+$, 16), 296
3c: Rf = 0.6 (hexane-ether = 1 : 1); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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, $J = 6.8$, 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); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (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, 1373, 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.

Typical experimental procedure (eq 3, Table 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%).

Diethyl 2-[trans-4-(1-chlorovinyl)-2-oxotetrahydrofuran-3-yl]malonate (4a): Rf = 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 $\delta$ 5.38 (=CH/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, 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 \(\delta 5.82\) (=CH\(_2\)).; \(^{13}\)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), \(\delta 3.40\) (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]\(^+\) 349.0285, 351.0261 (calcd for C\(_{13}\)H\(_{18}\)BrO\(_6\) 349.0287, 351.0266).

**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); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \(\delta\) (ppm) 13.83 (q), 13.93 (q), 31.58 (d), 42.70 (d), 50.94 (d), 62.28 (t), 62.30 (t), 71.19 (t), 74.57 (d), 79.22 (s), 167.07 (s), 167.13 (s), 174.14 (s); \(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)) \(\delta\) (ppm) 0.89 (t, \(J = 7.1\) Hz, 3H), 1.06 (t, \(J = 7.1\) Hz, 3H), 1.63 (d, \(J = 2.6\) Hz, 1H), 3.15 (dd, \(J = 8.2, 5.7, 2.6, 1.5\) 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\(_2\)(CO\(_2\)Et)\(_2\)); \(^{13}\)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\(_2\)(CO\(_2\)Et)\(_2\)), 31.79 (C-4), 79.65 (C\(\equiv\)CH), between \(\delta 3.15\) (H-4) and \(\delta 43.07\) (C-3), 79.65
(C≡CH), 74.16 (C≡CH), between δ 3.68 (H-5b) and δ 31.79 (C-4), 43.07 (C-3), 79.65 (C≡CH) and between δ 3.25 (H-5a) and δ 79.65 (C≡CH); IR (neat) 3275, 2982, 1781, 1734, 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 C13H17O6 269.1025).

6: Rf = 0.3 (hexane-ether = 1 : 1); pale yellow oil; 1H NMR (400 MHz, CDCl₃) δ (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 (ddt, 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); 13C NMR (100.6 MHz, CDCl₃) δ (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 C13H19O7 287.1131).

Diethyl 2-[trans-4-(1-chloro-2-methylprop-1-enyl)-2-oxotetrahydrofuran-3-yl]malonate (4c): Rf = 0.4 (hexane-ether = 1 : 1); 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), 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 δ 4.49 (H-4) and δ 3.96 (CH(CO₂Et)₂); 13C NMR (100.6 MHz, CDCl₃) δ (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), 68.53 (t), 123.71 (s), 134.30 (s), 167.51 (s), 167.70 (s), 175.61 (s). Selected HMBC correlations are between δ 4.49 (H-4) and δ 42.53 (C-3), 68.53 (C-5), between δ 3.56 (H-3) and δ 41.08 (C-4), 123.71 (CCl=), δ 4.39 (H-5b) and δ 42.53 (C-3), 68.53 (C-5), and between δ 1.79, 1.86 (=C(CH₃)₂) and δ 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 (calcd for C₁₅H₁₉ClO₆ 332.1027, 334.0997).

Diethyl 2-[trans-4-(1-bromo-2-methylprop-1-enyl)-2-oxotetrahydrofuran-3-yl]malonate (4d): Rf = 0.5 (hexane-ether = 1 : 1); pale yellow oil; 1H NMR (400 MHz, CDCl₃) δ (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, \(\text{C}_6\text{D}_6\)) \(\delta\) (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))_.

\(^{13}\)C NMR (100.6 MHz, \(\text{C}_6\text{D}_6\)) \(\delta\) (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)), 42.35 (C-4), between \(\delta\) 4.44 (H-4) and \(\delta\) 49.55 (CH(CO\(_2\)Et)), 44.01 (C-3), 69.89 (C-5), between \(\delta\) 4.08 (CH(CO\(_2\)Et)) 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, 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-**(trans-4-ethyl-2-oxotetrahydrofuran-3-yl)malonate (7t).** 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 7t (76 mg, 51%).

7t: \(R_f = 0.4\) (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), 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 ($CH_2CH_3$) and $\delta$ 44.79 (C-3), 39.34 (C-4), 71.91 (C-5) and between $\delta$ 0.917 ($CH_2CH_3$) 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 7t.** A solution of compound 8$^{11}$ (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 7t (89 mg, 89%). $^1$H NMR spectra of the product is identical with those of 7t obtained from 4a.

**Diethyl 2-(cis-4-ethyl-2-oxotetrahydrofuran-3-yl)malonate (7c).** 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 7c (115 mg, 78%).

7c: $R_f = 0.3$ (hexane-ether = 1 : 1); colorless oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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$_3$) $\delta$ (ppm) 11.36 (q), 13.97 (q), 14.04 (q), 20.34 (t), 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$_6$) $\delta$ (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 $\delta$ 3.65 ($CH(CO_2Et)_2$) and $\delta$ 0.698-0.814, 0.918-1.02 ($CH_2CH_3$); $^{13}$C NMR (100.6 MHz, C$_6$D$_6$) $\delta$ (ppm) 11.08 (q), 13.86 (q), 13.96 (q),
20.27 (t), 39.60 (d), 44.11 (d), 49.76 (t), 61.78 (t), 61.97 (t), 69.47 (t), 167.51 (s), 167.61 (s), 175.46 (s). Selected HMBC correlations are between $\delta$ 3.65 (CH(CO2Et)$_2$), 3.49 (H-5) and $\delta$ 44.11 (C-3), between $\delta$ 0.451 (CH$_2$C$_3$H$_7$), 0.698-0.814 (C$_6$H$_{12}$CH$_3$) and $\delta$ 39.60 (C-4), and between $\delta$ 0.698-0.814, 0.918-1.02 (CH$_2$C$_3$H$_7$) 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.$^{24}$ 10b was prepared according to the literature 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 ethenetricarboxylate (432 mg, 2 mmol) (prepared from 1,1-diethyl 2-tert-butyl ethenetricarboxylate (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 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 : 1) to give 11a (375 mg, 53%).
11a: \( R_f = 0.3 \) (hexane-ether = 1 : 1); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) (2 rotamers, ratio 1.5 : 1) \( \delta \) (ppm) 1.29 (t, \( J = 7.1 \) Hz, 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), 7.22-7.43 (m, 5H), 7.34 (s, 1H×0.4), 7.36 (s, 1H×0.6); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (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), 164.59 (s), 208.90 (s), 209.69 (s); IR (neat) 2983, 1956, 1732, 1652, 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 C\(_{20}\)H\(_{23}\)NO\(_5\) 357.1576).

11b (82%): \( R_f = 0.3 \) (hexane-ether = 1 : 1); pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) (2 rotamers, ratio 1 : 1) \( \delta \) (ppm) 0.909 (t, \( J = 7.4 \) Hz, 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 (ddd, \( J = 7.6 \), 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); \(^{13}\)C NMR (100.6 MHz, CDCl\(_3\)) \( \delta \) (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, 2956, 1729, 1652, 1466, 1445, 1430, 1374, 1256, 1210, 1068 cm\(^{-1}\); MS (EI) \( m/z \) 309 (M\(^+\), 43), 199 (48), 171 (63), 143 (100%); HRMS M\(^+\) 309.1581 (calcd for C\(_{16}\)H\(_{23}\)NO\(_5\) 309.1576).
Experimental procedure (eq 5, Table 2, entry 2). 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%).

Diethyl 2-(1-benzyl-trans-4-(1-chlorovinyl)-2-oxopyrrolidin-3-yl)malonate (12a): Rₜ = 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 (dd, 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 (=CH₂H) and between δ 3.72 (H-4) and δ 4.06 (CH(CO₂Et)₂); 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): Rₜ = 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 (dd, 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 (C(H(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, 1293, 1263, 1176, 1030 cm⁻¹; MS (EI) m/z 439 (M+, 34), 437 (M+, 38), 358 (23), 239 (34), 205 (62), 91 (100%); HRMS M⁺ 437.0835, 439.0826 (calcd for C20H24BrNO5 437.0838, 439.0817).

Diethyl 2-(1-benzyl-trans-4-(1-iodovinyl)-2-oxopyrrolidin-3-yl)malonate (12c): Rf = 0.6 (hexane-ether = 1 : 4); yellow oil; 1H NMR (400 MHz, CDCl3) δ (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 = 9.8, 7.1 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); 13C NMR (100.6 MHz, CDCl3) δ (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); 1H NMR (400 MHz, C6D6) δ (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 (dd, 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 δ 3.30 (H-3) and δ 5.81 (=CHH) and between δ 3.20 (H-4) and δ 4.31 (CH(CO2Et)2).

13C NMR (100.6 MHz, C6D6) δ (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 $\delta$ 3.30 (H-3) and $\delta$ 50.23 (CH(CO$_2$Et)$_2$), 46.45 (C-4), between $\delta$ 3.20 (H-4) and $\delta$ 50.23 (CH(CO$_2$Et)$_2$), 47.24 (C-3), between $\delta$ 2.86, 2.98 (H-5a,5b) and $\delta$ 116.56 (Cl=CH$_2$), and between $\delta$ 4.31 (CH(CO$_2$Et)$_2$) and $\delta$ 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 C$_{20}$H$_{25}$INO$_5$ 486.0778).

Diethyl 2-(trans-4-(1-chlorovinyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (12d): $R_f$ = 0.5 (hexane-ether = 1 : 2); pale yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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 $\delta$ 3.21-3.33 (H-3, overlapped) and $\delta$ 5.30 (=CHH) and between $\delta$ 3.74 (H-4) and $\delta$ 4.01 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (ppm) 11.18 (q), 13.95 (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 $\delta$ 3.21-3.33 (H-3, overlapped) and $\delta$ 50.12 (CH(CO$_2$Et)$_2$), 42.57 (C-4), between $\delta$ 3.74 (H-4) and $\delta$ 50.12 (CH(CO$_2$Et)$_2$), 44.71 (C-3), between $\delta$ 3.40, 3.54 (H-5a,5b) and $\delta$ 141.81 (CCl=CH$_2$), and between $\delta$ 4.01 (CH(CO$_2$Et)$_2$) and $\delta$ 44.71 (C-3), 42.57 (C-4); IR (neat) 2966, 2936, 1733, 1696, 1632, 1491, 1446, 1373, 1264, 1175, 1034 cm$^{-1}$; MS (FAB) $m/z$ 370 [M+Na]$^+$, 368 [M+Na]$^+$, 348 [M+H]$^+$, 346 [M+H]$^+$; HRMS [M+H]$^+$ 346.1421, 348.1392 (calcd for C$_{16}$H$_{25}$ClNO$_5$ 346.1421, 348.1392).

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×2), 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), 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, 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$_{24}$BrNO$_5$ 389.0838, 391.0817).

Diethyl 2-(trans-4-(1-iodovinyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (12f): $R_f = 0.6$ (hexane-ether = 1 : 4); yellow oil; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ (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); $^{13}$C NMR (100.6 MHz, CDCl$_3$) $\delta$ (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); $^1$H NMR (400 MHz, C$_6$D$_6$) $\delta$ (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 $\delta$ 3.22 (H-3, overlapped) and $\delta$ 5.93 (=CHH) and between $\delta$ 3.27 (H-4, overlapped) and $\delta$ 4.28 (CH(CO$_2$Et)$_2$); $^{13}$C NMR (100.6 MHz, C$_6$D$_6$) $\delta$ (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 $\delta$ 3.22 (H-3) and $\delta$ 50.29 (CH(CO$_2$Et)$_2$), 117.08 (Cl=CH$_2$), between $\delta$ 3.27 (H-4) and $\delta$ 51.48 (C-5), between $\delta$ 2.92, 3.01-3.10 (H-5a,5b) and $\delta$ 46.33 (C-4), and between $\delta$ 4.28 (CH(CO$_2$Et)$_2$) and $\delta$ 47.42 (C-3), 46.33 (C-4).; IR (neat) 2966, 2934, 1733, 1695, 1612, 1489, 1446, 1372, 1287, 1175, 1112, 1043 cm$^{-1}$; MS (EI) m/z 437 (M$^+$, 38), 392 (38), 310 (100%); HRMS M$^+$ 437.0697 (calcd for C$_{16}$H$_{24}$INO$_5$ 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 CH₃CN (1.4 mL), CCl₄ (1.4 mL), and H₂O (1.4 mL). NaIO₄ (385 g, 1.8 mmol) was then added followed by RuCl₃·xH₂O (5.2 mg, ca. 0.025 mmol). After 1 h of stirring at room temperature, the solution was diluted with CH₂Cl₂. The layers were separated, and the aqueous layer was extracted with CH₂Cl₂ three times. The combined organic layers were dried (Na₂SO₄) 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%).

13: Rf = 0.4 (hexane-ether = 1 : 4); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.52 (dd, J = 9.2, 4.4 Hz, 1H), 3.82 (ddd, J = 9.2, 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 δ 3.82 (H-4) and δ 4.07 (CH(CO₂Et)₂); ¹³C NMR (100.6 MHz, CDCl₃) δ (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 δ 3.52 (H-3) and δ 176.02 (CO₂H), 42.66 (C-4), between δ 3.82 (H-4) and δ 50.56 (CH(CO₂Et)₂), 41.82 (C-3), between δ 4.37, 4.69 (H₅a,₅b) and δ 176.02 (CO₂H), and between δ 4.07 (CH(CO₂Et)₂) and δ 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 C₁₂H₁₆O₈ 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 (CH₃)₃SiCHN₂ (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%).

14: Rf = 0.4 (hexane-ether = 1 : 1); colorless oil; ¹H NMR (400 MHz, CDCl₃) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 3.53 (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(CO2Et)2).

\(^{13}\)C NMR (100.6 MHz, CDCl3) \(\delta\) (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 (CO2CH3), 42.75 (C-4), between \(\delta\) 3.80 (H-4) and \(\delta\) 50.48 (CH(CO2Et)2), 41.97 (C-3), between \(\delta\) 4.28, 4.65 (H-5a,5b) and \(\delta\) 171.72 (CO2CH3), and between \(\delta\) 4.05 (CH(CO2Et)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 \(\mu\)L, 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%).

15a: \(R_f = 0.3\) (hexane-ether = 1 : 4); colorless needles; mp 119-121 °C (AcOEt-hexane); \(^1\)H NMR (400 MHz, CDCl3) \(\delta\) (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, CDCl3) \(\delta\) (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 \(\delta\) 3.51 (H-3) and \(\delta\) 170.14 (CONH), 44.14 (C-4), between \(\delta\) 3.61 (H-4) and \(\delta\) 50.35 (CH(CO2Et)2), 42.64 (C-3), and between \(\delta\) 4.45, 4.52 (H-5a,5b) and \(\delta\) 170.14 (CONH). IR (KBr) 3302, 2979, 1783.
1770, 1731, 1646, 1540, 1371, 1258, 1189, 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 C₁₉H₂₃NO₇ 377.1475).

15b: Rᵣ = 0.5 (hexane-ether = 1 : 4); colorless needles; mp 118-120 °C (benzene); ¹H NMR (400 MHz, CDCl₃) δ (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); ¹³C NMR (100.6 MHz, CDCl₃) δ (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 δ 3.51 (H-3) and δ 170.24 (CONH), 44.09 (C-4), between δ 3.63 (H-4) and δ 50.31 (CH(CO₂Et)₂), 42.48 (C-3), and between δ 4.39, 4.52 (H-5a,5b) and δ 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 C₁₉H₂₂ClNO₇ 411.1085, 413.1055); Anal. Calcd for C₁₉H₂₂ClNO₇: C, 55.41; H, 5.38; N, 3.40. Found: C, 55.26; H, 5.15; N, 3.32.

Preparation of 16a-b (eq 6). To a mixture of phenylboronic acid (39 mg, 0.323 mmol), 12c (155 mg, 0.307 mmol), K₂CO₃ (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 (Na₂SO₄), and evaporated in vacuo. The residue was purified by column chromatography over silica gel eluting with hexane-ether to give 16a (78 mg, 58%).

16a: Rᵣ = 0.6 (hexane-ether = 1 : 4); pale yellow oil; ¹H NMR (400 MHz, CDCl₃) 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(CO2Et)2); 13C NMR (100.6 MHz, CDCl3) 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(CO2Et)2), 39.38 (C-4), between δ 3.77 (H-4) and δ 51.01 (CH(CO2Et)2), 45.71 (C-3), between δ 3.00, 3.48 (H-5a,5b) and δ 148.69 (CPh=CH2), and between δ 3.96 (CH(CO2Et)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 C26H29NO5 435.2046).

16b: Rf = 0.4 (hexane-ether = 1 : 4); colorless oil; 1H NMR (400 MHz, CDCl3) δ (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 (dddd, 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 δ 3.36 (H-3) and δ 5.16 (=CHH), 7.28-7.35 (Ph), and between δ 3.79 (H-4) and δ 3.92 (CH(CO2Et)2); 13C NMR (100.6 MHz, CDCl3) δ (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 δ 3.36 (H-3) and δ 51.09 (CH(CO2Et)2), 39.37 (C-4), between δ 3.79 (H-4) and δ 51.09 (CH(CO2Et)2), 45.85 (C-3), and between δ 3.92 (CH(CO2Et)2) and δ 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 C22H29NO5 387.2046).
Acknowledgment

This work was supported by the Ministry of Education, Culture, Sports, Science, and Technology of the Japanese Government. We thank Nara Institute of Science and Technology (NAIST) and Prof. K. Kakiuchi (NAIST) for mass spectra.

Electronic supplementary information (ESI) available: The optimized geometries, and $^1$H and $^{13}$C NMR spectral data.

References


