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Lewis Acid-Promoted Cyclization/Halogenation of Allenyl Ethenetricarboxylates and the Amides: Stereoselective Synthesis of Haloalkenyl Five-membered Heterocycles

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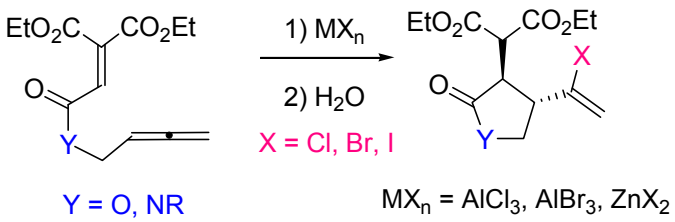
Graphical Abstract



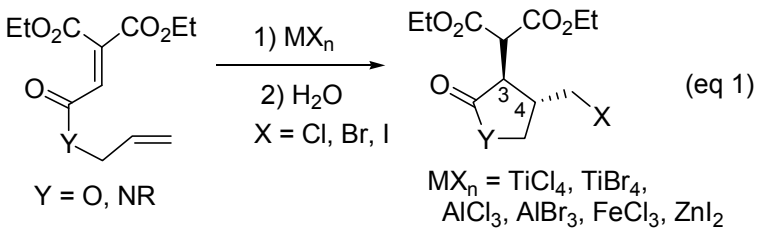
Abstract: Lewis acid-promoted intramolecular reactions of allenyl ethenetricarboxylates and the corresponding amides have been examined. Reaction of allenyl ethenetricarboxylates and the amides with Lewis acids such as $AlCl_3$, $AlBr_3$ and ZnX_2 (X = Cl, Br, I) gave 3,4-*trans* haloalkenyl five-membered 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,[3] photochemical,[4] reductive[5] and base-promoted[6] cyclization reactions of these allenes have been reported. Lewis acid-promoted carbon-carbon bond-forming cyclizations of allenyl-aldehyde actetals[7] and aryl-allenes[8] 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.[9] We have developed Lewis acid-promoted stereoselective cyclization of alkynyl ethenetricarboxylates with high generality[10] and Lewis acid-promoted 3,4-*trans* stereoselective cyclization of alkenyl ethenetricarboxylates has also been investigated (eq 1).[11]



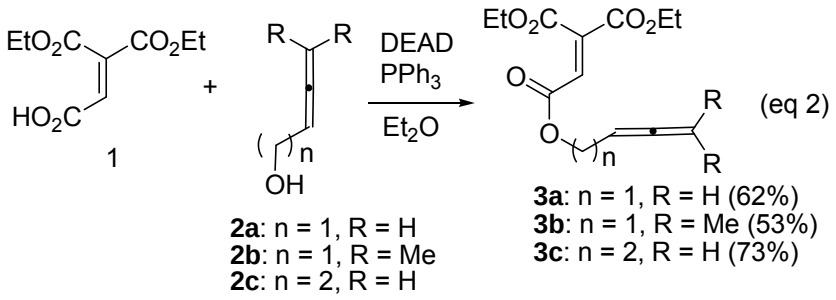
(eq 1)

We have studied various Lewis acid-promoted intermolecular reactions of ethenetricarboxylate derivatives and reported that they function as highly electrophilic Michael acceptors.[12] The reaction of arylallenes and ethenetricarboxylate with $SnCl_4$ gave indene derivatives efficiently.[13] In addition, the reactions of 1,1-dialkylallenes and ethenetricarboxylate with $SnCl_4$ 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.[14]

Results and Discussion

Allenyl esters **3a-c** were prepared by the reaction of 1,1-diethyl 2-hydrogen ethenetricaboxylate **1** (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate upon treatment with CF_3CO_2H) with the corresponding allenyl alcohols **2a-c** in the presence of PPh_3 and DEAD (diethyl azodicarboxylate) (eq 2).



The reaction of allenyl ethenetricarboxylates **3a,b** with 1 equivalent of various Lewis acid such as $AlCl_3$, $AlBr_3$, $SnCl_4$, $TiCl_4$, $FeCl_3$, $InCl_3$, or $InBr_3$ in CH_2Cl_2 at room temperature gave 3,4-*trans* haloalkenyl tetrahydrofuran derivatives **4a-d** stereoselectively (eq 3, Table 1). Among these Lewis acids, $AlCl_3$ and $AlBr_3$ gave chlorinated and brominated cyclic products **4a-d** most efficiently. The reaction of **3a** with $SnCl_4$, $TiCl_4$ and $TiBr_4$ also gave **4a,b** along with 4-ethynyltetrahydrofuran derivative **5** as a by-product via Lewis acid-catalyzed ene-type reaction. Use of $FeCl_3$, $InCl_3$ and $InBr_3$ gave **4a,b** and the noncyclized H_2O adduct **6** as a by-product (entries 6-8). Furthermore, the reaction of **3a** using $ZnBr_2$, $BF_3{\cdot}OEt_2$, $ZrCl_4$, and $Zn(OTf)_2$ at room temperature gave the starting material **3a**. The reaction of **3a** with $ZnBr_2$, ZnI_2, $Sc(OTf)_3$, and $Zn(OTf)_2$ at 80 °C gave a complex mixture or the starting material **3a**.

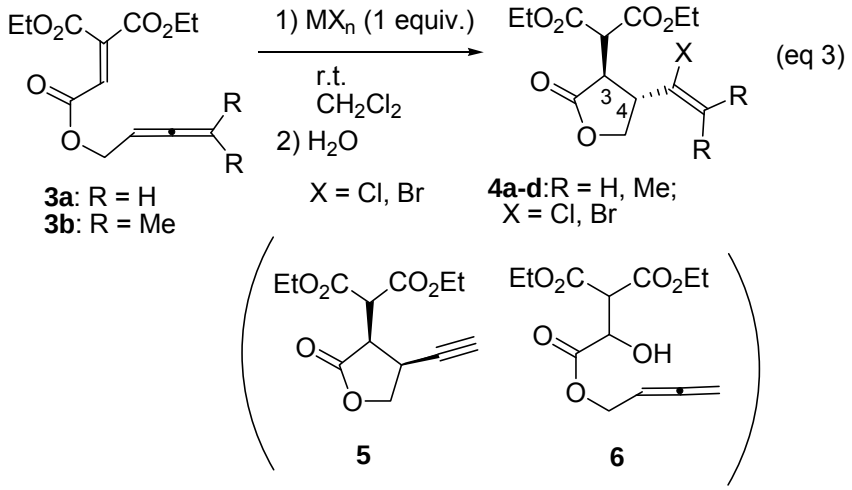


Table 1. Reactions of Allenyl Esters **3a,b**

Entry	**3**	R	MX_n	Time (h)	**4**	X	Yield (%)	Byproduct (%)
1	**3a**	H	$AlCl_3$	18	**4a**	Cl	75	
2	**3a**	H	$AlBr_3$	18	**4b**	Br	64	
3	**3a**	H	$SnCl_4$	3	**4a**	Cl	42	**5** (ca. 19)[a]

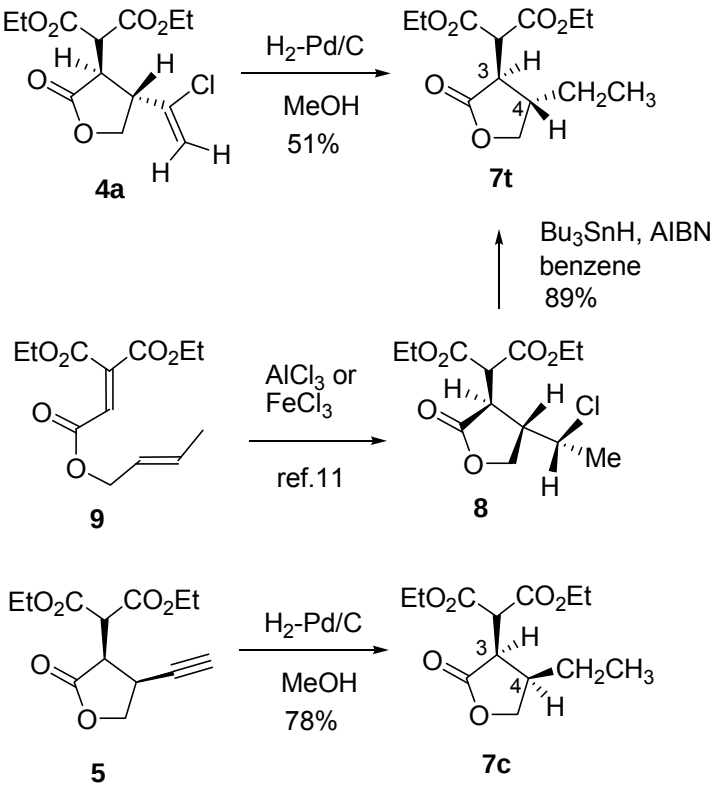
4	**3a**	H	$TiCl_4$	3	**4a**	Cl	58	**5** (ca. 18)[a]
5	**3a**	H	$TiBr_4$	18	**4b**	Br	46	**5** (30)
6	**3a**	H	$FeCl_3$	3	**4a**	Cl	36[b]	**6** (54)[b]
7	**3a**	H	$InCl_3$	18	**4a**	Cl	12	**6** (20), **3a** (44%)
8	**3a**	H	$InBr_3$	18	**4b**	Br	40	**6** (36)
7	**3b**	Me	$AlCl_3$	18	**4c**	Cl	66	
8	**3b**	Me	$AlBr_3$	18	**4d**	Br	44	
9	**3b**	Me	$SnCl_4$	18	**4c**	Cl	30	[c]

[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=C allene moiety in **3a,b**. ^1H, ^{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-*cis* and *trans* diastereomers. The following peaks were used for the assignment of haloalkenyl 2-oxotetrahydrofurans **4a-d**. NOEs between H-3 and CX=CH*H* (X = Cl, Br)[15] for **4a,b** and between H-4 and C*H*$(CO_2Et)_2$ 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-ethynyltetrahydrofuran **5** did not give enough information for the 3,4-stereochemistry.

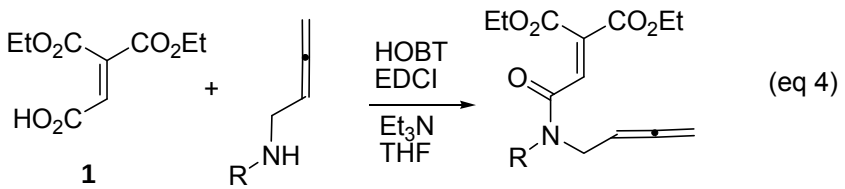
In order to support the assignment of the stereochemistry of **4a** and determine the stereochemistry of the by-product 4-ethynyltetrahydrofuran **5**, the following transformations have been carried out. Hydrogenolysis of the 4-chlorovinyl-2-oxotetrahydrofuran **4a** gave 3,4-*trans*-4-ethyl-2-oxotetrahydrofuran **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 Bu_3SnH 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**

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 $AlCl_3$, $AlBr_3$, and $SnCl_4$ gave complex mixtures. Six-membered ring formation was not an efficient process.



10a: R = CH_2Ph **11a**: R = CH_2Ph (53%)
10b: R = $CH_2CH_2CH_3$ **11b**: R = $CH_2CH_2CH_3$ (82%)

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_3N (eq 4). 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 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 $AlBr_3$ also gave **12b**,**e** but 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}). ^1H, ^{13}C 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=C*H*H (X = Cl, Br, I)[15] and between H-4 and C*H*$(CO_2Et)_2$ were observed.

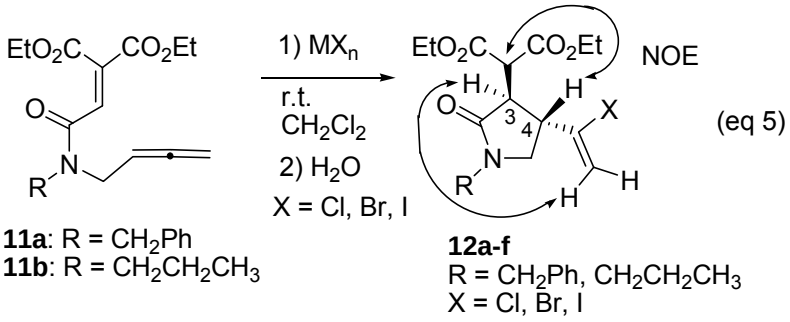
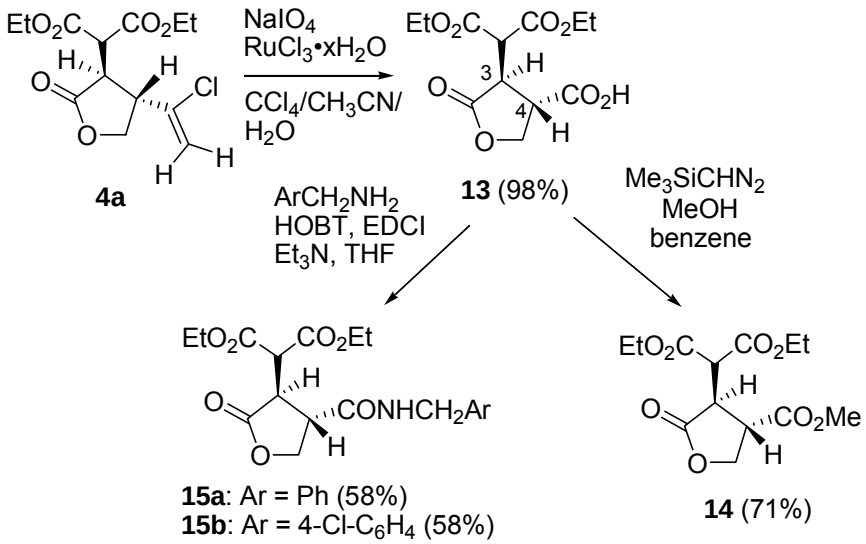


Table 2. Reactions of Allenyl Amides **11**

Entry	R	MX_n	(equiv.)	X	**12**	Yield (%)
1	CH_2Ph	$AlCl_3$	1	Cl	**12a**	55
2	CH_2Ph	$ZnCl_2$ [a]	1×2	Cl	**12a**	76
3	CH_2Ph	$ZnBr_2$ [a]	1×2	Br	**12b**	64
4	CH_2Ph	ZnI_2	2	I	**12c**	58
5	$CH_2CH_2CH_3$	$AlCl_3$	1	Cl	**12d**	68
6	$CH_2CH_2CH_3$	$ZnBr_2$ [a]	1×2	Br	**12e**	64
7	$CH_2CH_2CH_3$	ZnI_2 [a]	1×2	I	**12f**	68

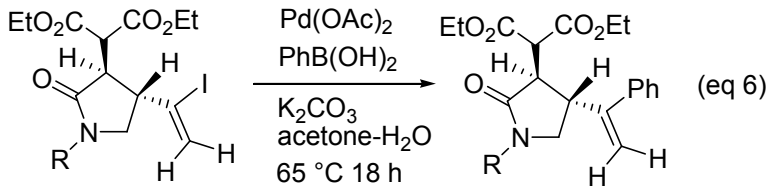
a. The reaction with ZnX_2 (1 equiv) for 18 h gave the crude products including impurities (possibly non-cyclized water-adducts) after work-up. The crude products were further treated with ZnX_2 (1 equiv) to give the products **12**.

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 $NaIO_4$-$RuCl_3 \cdot xH_2O$ and a neutral work-up gave acid **13** in 98% yield (Scheme 2). Subsequent treatment of **13** with Me_3SiCHN_2 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**.



Scheme 2. Transformation of **4a**

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).



(eq 6)

12c: R = CH_2Ph
12f: R = $CH_2CH_2CH_3$

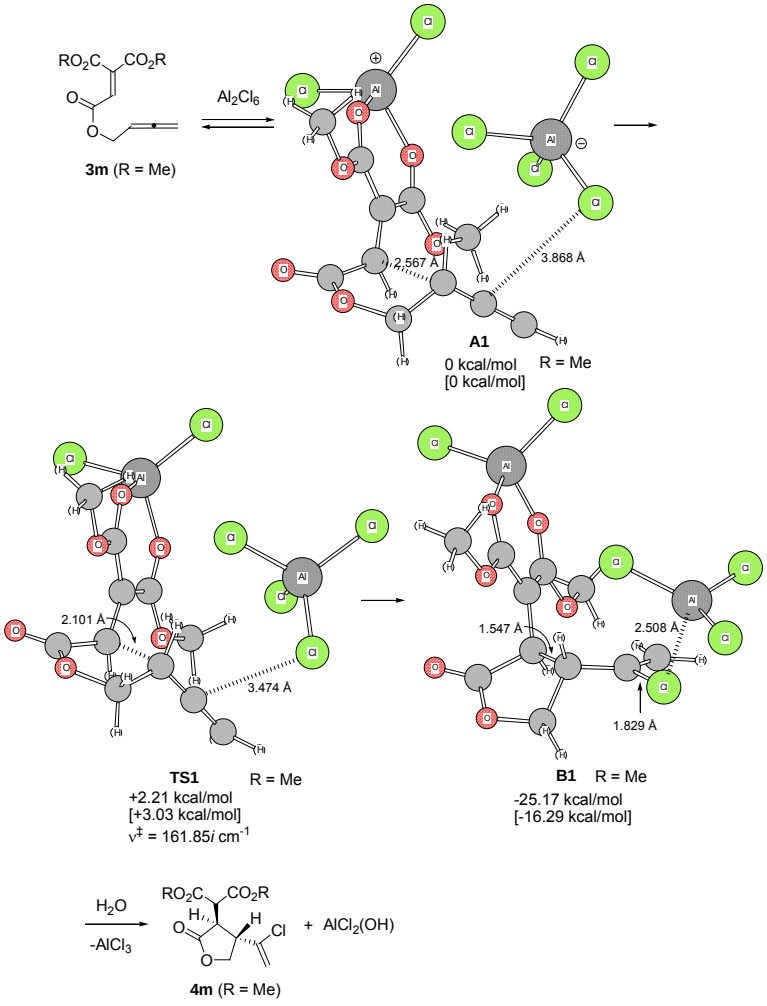
16a: R = CH_2Ph (58%)
16b: R = $CH_2CH_2CH_3$ (63%)

The reaction mechanism to give the halogenated five-membered heterocycles with 3,4-*trans* stereochemistry is proposed similar to that for the reaction of the allyl ester of ethenetrcarboxylates (eq 1)[11] and shown in Scheme 3. *Trans* precursor **A1** and *cis* precursor **A2** in Scheme 4 may be formed from **3** and Al_2Cl_6 reversibly. The reaction may start from the precursor **A1** consisting of **3** and Al_2Cl_6. The C-C bond formation and Cl-C bond formation from **A1** may occur concertedly to lead to cyclized intermediate **B1**. Intermolecular Cl^- anti attack leading to 3,4-*trans* cyclized product can be explained by steric reason. One molecule of Lewis acid ($AlCl_3$) may work as a catalyst and could be released after the cyclization step. Protonation and removal of $AlCl_2(OH)$ yield the product **4**.

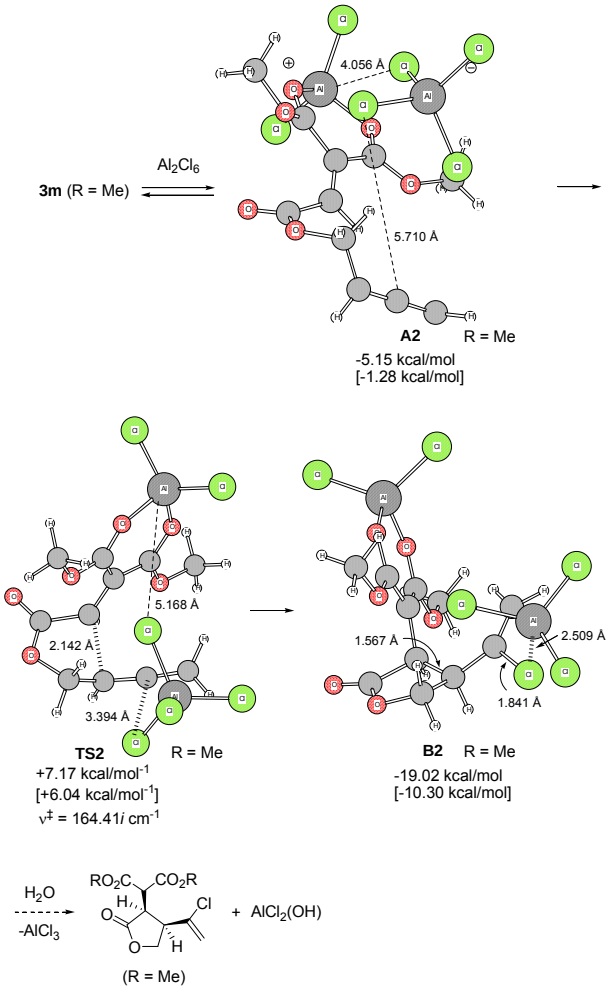
In order to support the proposed mechanism, the structures of the intermediates and transition states of model compounds (the corresponding methyl esters and Al_2Cl_6) were calculated using B3LYP/6-31G*.[17,18] TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has single imaginary frequencies ($v^‡$). From TSs, reaction paths were traced by the intrinsic reaction coordinate (IRC) method[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_2Cl_2)[20] on the RB3LYP/6-31G* geometries and their thermal corrections (T = 298.15 K, P = 1 atm). $\Delta G^‡$ for TS1 leading to 3,4-*trans* tetrahydrofuran is found to be lower than that of TS2 leading to 3,4-*cis* tetrahydrofuran (Schemes 3,4). Two conformational isomers, *trans* precursor **A1** and *cis* precursor **A2** were obtained. **A2** is 5.15 [1.28] kcal/mol more stable than **A1**. 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[21] may be applicable in this case. The calculation results are similar to those for allyl

ester + Al_2Cl_6.[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**.

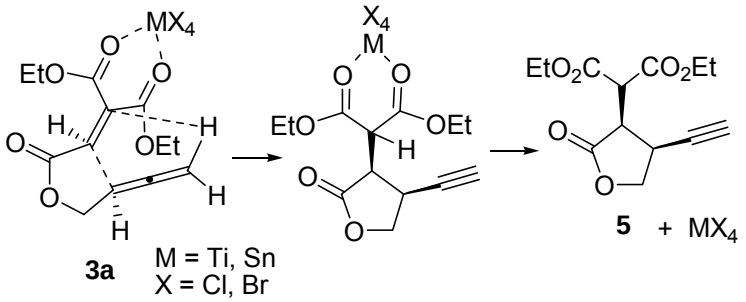
Calculations of 1:1 complex of the substrate and $AlCl_3$ were also examined (Supplementary Information). Although the concerted formations of both 3,4-*cis* and *trans* tetrahydrofuran rings by intramolecular Cl^- attack were calculated, they have higher activation energies ($\Delta G^{\ddagger}$) than the systems of the substrate and Al_2Cl_6. In addition, the $AlCl_3$-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 ($\Delta G^{\ddagger}$) for formation of **5** with $AlCl_3$ is also higher than the systems of the substrate and Al_2Cl_6. Further mechanistic studies are underway.



Scheme 3. Proposed reaction mechanism for cyclization of alleyl ester model compound **3m** (R = Me) with Al_2Cl_6. Relative Gibbs free energies (T = 298.15 K and P = 1 atm) for intermediates and TSs (transition states) of the model compounds (**3m** + Al_2Cl_6) are obtained by B3LYP/6-31G* (without brackets) and [B3LYP/6-311+G(d,p) SCRF = (PCM, solvent = CH_2Cl_2) // B3LYP/6-31G*] (with square brackets [ ]).

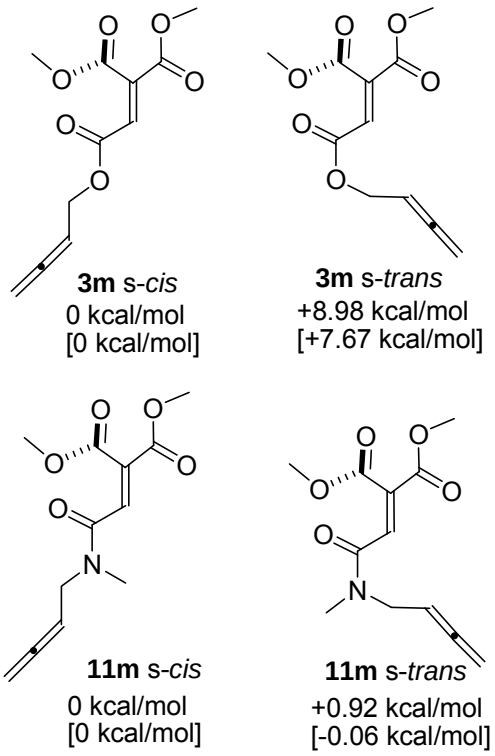


Scheme 4. The reaction pathway leading to 3,4-*cis* intermediate **B2** for model compounds (**3m** + Al_2Cl_6). B3LYP/6-31G*-optimized structures of the model compounds are shown. The Gibbs free energies are relative to **A1** (R = Me) in Scheme 3.



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* conformarions 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 ΔG^{o}. ΔG^{o} 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_2Cl_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-contaning 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_4Si. ^{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_3CO_2H) 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, $CDCl_3$) δ (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); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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), 171 (95), 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, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 ($(M+1)^+$, 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; ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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, 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_2Cl_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_2SO_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): R_f = 0.7 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (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 δ 3.43 (H-3) and δ 5.38 (=CH*H*).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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 δ 3.97 (H-4) and δ 41.85 (C-3), 68.74 (C-5), between δ 3.43 (H-3) and δ 46.09 (C-4), 138.72 (*C*Cl=), δ 4.52 (H-5b) and δ 41.85 (C-3), 138.72 (*C*Cl=), and between δ 5.32, 5.38 (=CH_2) and δ 46.09 (C-4), 138.72 (*C*Cl=); 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; ^1H NMR (400 MHz, $CDCl_3$) δ (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 δ 3.40 (H-3) and 5.82 (=CH*H*).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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 δ 3.87 (H-4) and δ 42.87 (C-3), 121.67 (=*C*H_2), between δ 3.40 (H-3) and δ 47.42 (C-4), 131.71 (*C*Br=), δ 4.49 (H-5b) and δ 42.87 (C-3), 131.71 (*C*Br=), and between δ 5.57, 5.82 (=CH_2) and δ 47.42 (C-4), 131.71 (*C*Br=); 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; ^1H NMR (400 MHz, $CDCl_3$) δ (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, $CDCl_3$) δ (ppm) 14.01 (q), 14.04 (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); ^1H NMR (400 MHz, C_6D_6) δ (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 δ 3.15 (H-4) and δ 3.42 (H-3), 3.25 (H-5a) and between δ 3.42 (H-3) and δ 4.09 (C*H*$(CO_2Et)_2$).; ^{13}C NMR (100.6 MHz, C_6D_6) δ (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 δ 3.42 (H-3) and δ 51.41 (*C*H$(CO_2Et)_2$), 31.79 (C-4), 79.65 (*C*≡CH), between δ 3.15 (H-4) and δ 43.07 (C-3), 79.65

(*C*≡CH), 74.16 (C≡*C*H), 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 $C_{13}H_{17}O_6$ 269.1025).

6: R_f = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) 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 (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, $CDCl_3$) 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 (CI) *m/z* 287 $[M+H]^+$; HRMS $[M+H]^+$ 287.1130 (calcd for $C_{13}H_{19}O_7$ 287.1131).

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; ^1H NMR (400 MHz, $CDCl_3$) 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 (C*H*$(CO_2Et)_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*Cl=), δ 4.39 (H-5b) and δ 42.53 (C-3), 68.53 (C-5), and between δ 1.79, 1.86 (=C(CH_3)$_2$) and δ 123.71 (*C*Cl=).; 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 $C_{15}H_{21}ClO_6$ 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; ^1H NMR (400 MHz, $CDCl_3$) 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, $CDCl_3$) δ (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_6D_6) δ (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 δ 4.44 (H-4) and δ 4.08 (C*H*$(CO_2Et)_2$).; ^{13}C NMR (100.6 MHz, C_6D_6) δ (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 δ 3.51 (H-3) and δ 49.55 (*C*H$(CO_2Et)_2$), 42.35 (C-4), between δ 4.44 (H-4) and δ 49.55 (*C*H$(CO_2Et)_2$), 44.01 (C-3), 69.89 (C-5), between δ 4.08 (C*H*$(CO_2Et)_2$) and δ 44.01 (C-3), 42.35 (C-4), and between δ 1.53, 1.57 (=C(C*H*$_3$)$_2$) and δ 119.68 (*C*Br=).; 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-(*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, $CDCl_3$) δ (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 δ 2.87 (H-3) and δ 0.917 (CH_2CH_3), 1.37-1.50, 1.61-1.71 (CH_2CH_3), and between δ 2.60 (H-4) and δ 3.90 (C*H*$(CO_2Et)_2$, overlapped).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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 δ 1.37-1.50, 1.61-1.71 (CH_2CH_3) and δ 44.79 (C-3), 39.34 (C-4), 71.91 (C-5) and between δ 0.917 (CH_2CH_3) and δ 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_3SnH (215 mg, 199 μL, 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 presure. 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, $CDCl_3$) 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_6D_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 ($CH(CO_2Et)_2$) and δ 0.698-0.814, 0.918-1.02 (CH_2CH_3).;^{13}C NMR (100.6 MHz, C_6D_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 (C*H*($CO_2Et)_2$), 3.49 (H-5) and δ 44.11 (C-3), between δ 0.451 (CH_2CH_3), 0.698-0.814 (C*H*HCH_3) and δ 39.60 (C-4), and between δ 0.698-0.814, 0.918-1.02 (CH_2CH_3) and δ 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, $CDCl_3$) δ (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, $CDCl_3$) δ (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 $C_7H_{14}N$ 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_3CO_2H) in THF (2.8 mL) were added allenylamine **10a** (326 mg, 2 mmol), Et_3N (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_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_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) 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), 7.22-7.43 (m, 5H), 7.34 (s, 1H×0.4), 7.36 (s, 1H×0.6); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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), 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) δ (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 (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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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, 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 CH_2Cl_2 (2 mL) was added $ZnCl_2$ (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 $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was dried (Na_2SO_4), and evaporated *in vacuo*. The crude product included impurities (possibly non-cyclized water-adducts). To a solution of the crude product in CH_2Cl_2 (2 mL) was added $ZnCl_2$ (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 $NaHCO_3$. The mixture was extracted with dichloromethane and the organic phase was dried (Na_2SO_4), 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): R_f = 0.3 (hexane-ether = 1 : 1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (=CH*H*) and between δ 3.72 (H-4) and δ 4.06 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*H(CO_2Et)$_2$), 42.64 (C-4), between δ 3.72 (H-4) and δ 50.09 (*C*H(CO_2Et)$_2$), 44.58 (C-3), between δ 3.29, 3.41 (H-5a,5b) and δ 141.52 (*C*Cl=CH_2), and between δ 4.06 (C*H*(CO_2Et)$_2$) 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 $C_{20}H_{24}ClNO_5$ 393.1345, 395.1314).

Diethyl 2-(1-benzyl-*trans*-4-(1-bromovinyl)-2-oxopyrrolidin-3-yl)malonate (12b): R_f = 0.6 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (=CH*H*) and between δ 3.63 (H-4) and δ 4.07 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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(CO_2Et)$_2$), 45.50 (C-3), between δ 3.26, 3.39 (H-5a,5b) and δ 134.80 (*C*Br=CH_2), and between δ 4.07 (C*H*(CO_2Et)$_2$) 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 (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 $C_{20}H_{24}BrNO_5$ 437.0838, 439.0817).

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, $CDCl_3$) 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* = 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, $CDCl_3$) 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); ^{1}H NMR (400 MHz, C_6D_6) 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 (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 δ 3.30 (H-3) and δ 5.81 (=CH*H*) and between δ 3.20 (H-4) and δ 4.31 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, C_6D_6) 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 δ 3.30 (H-3) and δ 50.23 (*C*H(CO_2Et)$_2$), 46.45 (C-4), between δ 3.20 (H-4) and δ 50.23 (*C*H(CO_2Et)$_2$), 47.24 (C-3), between δ 2.86, 2.98 (H-5a,5b) and δ 116.56 (*C*I=CH_2), and between δ 4.31 (C*H*(CO_2Et)$_2$) 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 $C_{20}H_{25}INO_5$ 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, $CDCl_3$) 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 (=CH*H*) and between δ 3.74 (H-4) and δ 4.01 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*H(CO_2Et)$_2$), 42.57 (C-4), between δ 3.74 (H-4) and δ 50.12 (*C*H(CO_2Et)$_2$), 44.71 (C-3), between δ 3.40, 3.54 (H-5a,5b) and δ 141.81 (*C*Cl=CH_2), and between δ 4.01 (C*H*(CO_2Et)$_2$) and δ 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, $CDCl_3$) δ (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 δ 3.20-3.34 (H-3, overlapped) and δ 5.74 (=CH*H*) and between δ 3.65 (H-4) and δ 4.01 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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), 167.96 (s), 168.17 (s), 171.53 (s). Selected HMBC correlations are between δ 3.20-3.34 (H-3, overlapped) and δ 50.04 (*C*H(CO$_2$Et)$_2$), between δ 3.65 (H-4) and δ 50.04 (*C*H(CO$_2$Et)$_2$), 45.63 (C-3), between δ 3.38, 3.53 (H-5a,5b) and δ 135.10 (*C*Br=CH$_2$), and between δ 4.01 (C*H*(CO$_2$Et)$_2$) and δ 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$_{24}$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$_3$) 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); ^{13}C NMR (100.6 MHz, CDCl$_3$) 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); ^{1}H NMR (400 MHz, C$_6$D$_6$) 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 (=CH*H*) and between δ 3.27 (H-4, overlapped) and δ 4.28 (C*H*(CO$_2$Et)$_2$).; ^{13}C NMR (100.6 MHz, C$_6$D$_6$) 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 (*C*H(CO$_2$Et)$_2$), 117.08 (*C*I=CH$_2$), between δ 3.27 (H-4) and δ 51.48 (C-5), between δ 2.92, 3.01-3.10 (H-5a,5b) and δ 46.33 (C-4), and between δ 4.28 (C*H*(CO$_2$Et)$_2$) 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^{-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 CH_3CN (1.4 mL), CCl_4 (1.4 mL), and H_2O (1.4 mL). $NaIO_4$ (385 g, 1.8 mmol) was then added followed by $RuCl_3 \cdot xH_2O$ (5.2 mg, ca. 0.025 mmol). After 1 h of stirring at room temperature, the solution was diluted with CH_2Cl_2. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 three times. The combined organic layers were dried (Na_2SO_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%).

13: R_f = 0.4 (hexane-ether = 1 : 4); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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 (C*H*$(CO_2Et)_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*O_2H), 42.66 (C-4), between δ 3.82 (H-4) and δ 50.56 (*C*H$(CO_2Et)_2$), 41.82 (C-3), between δ 4.37, 4.69 (H-5a,5b) and δ 176.02 (*C*O_2H), and between δ 4.07 (C*H*$(CO_2Et)_2$) 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 $C_{12}H_{16}O_8$ 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 $(CH_3)_3SiCHN_2$ (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%).

14: R_f = 0.4 (hexane-ether = 1 : 1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 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 δ 3.80 (H-4) and δ 4.05 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (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 δ 3.53 (H-3) and δ 171.72 (*C*O_2CH_3), 42.75 (C-4), between δ 3.80 (H-4) and δ 50.48 (*C*H(CO_2Et)$_2$), 41.97 (C-3), between δ 4.28, 4.65 (H-5a,5b) and δ 171.72 (*C*O_2CH_3), and between δ 4.05 (C*H*(CO_2Et)$_2$) and δ 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_3N (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 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_2Cl_2. The organic phase was washed with saturated aqueous $NaHCO_3$ solution, 2M aqueous citric acid, saturated aqueous $NaHCO_3$ and water, dried (Na_2SO_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 ºC (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 (*C*ONH), 44.14 (C-4), between δ 3.61 (H-4) and δ 50.35 (*C*H(CO_2Et)$_2$), 42.64 (C-3), and between δ 4.45, 4.52 (H-5a,5b) and δ 170.14 (*C*ONH).; 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 ºC (benzene); ^{1}H NMR (400 MHz, $CDCl_3$) 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); ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*ONH), 44.09 (C-4), between δ 3.63 (H-4) and δ 50.31 (*C*H(CO_2Et)$_2$), 42.48 (C-3), and between δ 4.39, 4.52 (H-5a,5b) and δ 170.24 (*C*ONH).; 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-b (eq 6). To a mixture of phenylboronic acid (39 mg, 0.323 mmol), **12c** (155 mg, 0.307 mmol), K_2CO_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_2SO_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%).

16a: 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 (=C*H*H), and between δ 3.77 (H-4) and δ 3.96 (C*H*(CO_2Et)$_2$).; ^{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 (*C*H(CO_2Et)$_2$), 39.38 (C-4), between δ 3.77 (H-4) and δ 51.01 (*C*H(CO_2Et)$_2$), 45.71 (C-3), between δ 3.00, 3.48 (H-5a,5b) and δ 148.69 (*C*Ph=CH_2), and between δ 3.96 (C*H*(CO_2Et)$_2$) 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, $CDCl_3$) 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 (=C*H*H), 7.28-7.35 (Ph), and between δ 3.79 (H-4) and δ 3.92 (C*H*(CO_2Et)$_2$).; ^{13}C NMR (100.6 MHz, $CDCl_3$) 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 (*C*H(CO_2Et)$_2$), 39.37 (C-4), between δ 3.79 (H-4) and δ 51.09 (*C*H(CO_2Et)$_2$), 45.85 (C-3), and between δ 3.92 (C*H*(CO_2Et)$_2$) 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 $C_{22}H_{29}NO_5$ 387.2046).

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

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