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Lewis Acid-Promoted Cyclization Reactions of Alkenyl Ethenetricarboxylates: Stereoselective Synthesis of 2-Oxotetrahydrofurans and 2-Oxopyrrolidines

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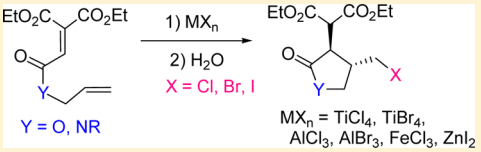
Supporting Information

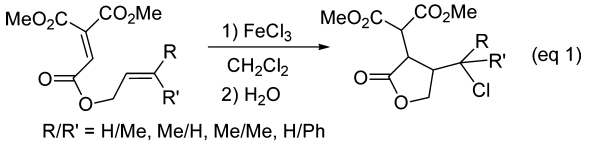
ABSTRACT: Lewis acid-promoted intramolecular reactions of alkenyl ethenetricarboxylates and the corresponding amides have been examined. Reaction of allyl ethenetricarboxylates and the amides with Lewis acids (1−2 equiv) such as $TiCl_4$, $TiBr_4$, $AlCl_3$, and $AlBr_3$ gave 3,4-*trans*-halogenomethyl 2-oxotetrahydrofuran and pyrrolidine derivatives stereoselectively in high yields. The stereochemistries were determined by NOE experiments. Reaction of alkyl-substituted allylic ethenetricarboxylates with Lewis acids gave chloro 2-oxotetrahydrofurans and pyrans. For some alkyl-substituted substrates, cationic intermediates may be formed under the reaction conditions, and rearranged products have been obtained.



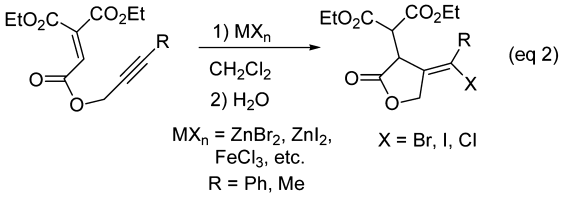
INTRODUCTION

Oxygen- and nitrogen-containing heterocyclic systems such as five-membered rings, tetrahydrofurans and pyrrolidines, are versatile core structures in organic chemistry because of their presence in many biologically active compounds.[1,2] The development of new efficient synthetic strategies for the construction of these heterocycles is of considerable interest.[3,4]

Snider and Roush reported that Lewis acid-promoted intramolecular reactions of alkenyl and alkynyl ethenetricarboxylates gave chlorinated γ-lactones (eq 1).[5] We have developed Lewis



(eq 1)



(eq 2)

acid-promoted stereoselective cyclization of alkynyl ethenetricarboxylates with high generality (eq 2).[6] Lewis acid-promoted intramolecular ene reaction[7] and related cyclization of silicon-substituted allylic alkylidene 1,3-dioxo compounds to give carbocycles[8] have also been reported. Furthermore, Lewis acid-promoted addition of simple alkenes to aldehydes proceeding to form C−C bonds (Prins reaction) is well-known.[9] However, few Lewis acid-promoted Michael additions of simple alkenes such as allyl moieties have been reported. Related Lewis acid-promoted reactions to give nitrogen-containing heterocycles may also be of interest.

We have studied various Lewis acid-promoted intermolecular reactions of ethenetricarboxylate derivatives and reported that they function as highly electrophilic Michael acceptors.[10] In this work, Lewis acid-promoted intramolecular reaction of alkenyl ester and amides of ethenetricarboxylate leading to five-membered heterocycles has been examined. Furthermore, the scope and limitation of the Lewis acid-promoted intramolecular reactions of alkyl-substituted allylic esters have been described.

RESULTS AND DISCUSSION

Cyclization of Alkenyl Ethenetricarboxylates and the Amides. 2-Allyl 1,1-diethyl ethene-1,1,2-tricarboxylate (**1**) was previously used in $TiCl_4$-promoted intermolecular reaction with aminoacetals.[10a] Competing intramolecular reaction was not observed under the reaction conditions. After examining various Lewis acids, it was found that reaction with $AlCl_3$, $AlBr_3$, $TiCl_4$, and $TiBr_4$ (1−2 equiv) at room temperature gave diethyl 2-(*trans*-4-(chloro (or bromo)methyl)-2-oxotetrahydrofuran-3-yl)-malonate (**2a**,**b**) in 57−90% yields (eq 3, Table 1). For $AlCl_3$, $TiCl_4$, and $TiBr_4$, use of 2 equiv of Lewis acids is required to drive the reaction to completion.

The γ-lactone structure of **2a**,**b** was suggested by the presence of a characteristic C=O absorption (1777−1779 cm^{-1}). ^1H, ^{13}C and 2D NMR spectra were in agreement with the five-membered ring structure. The 3,4-stereochemistry of **2a**,**b** 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 the obtained single

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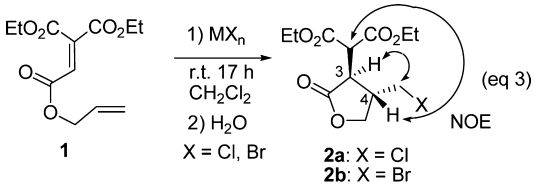
Table 1. Reactions of Allyl Ester 1

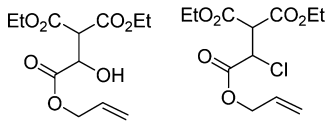
entry	MX_n	MX_n (equiv)	2	yield (%)
1	$AlCl_3$	1	**2a**	58[a]
2	$AlCl_3$	2	**2a**	72
3	$AlBr_3$	1	**2b**	57
4	$AlBr_3$	2	**2b**	45
5	$TiCl_4$	1	**2a**	[b]
6	$TiCl_4$	2	**2a**	90
7	$TiBr_4$	1	**2b**	[b]
8	$TiBr_4$	2	**2b**	62

[a]A small amount of the starting material **1** could not be removed. [b]The mixture including **1** and **2a**/**2b** was obtained and could not be purified.

diastereomer. NOEs between H-3 and C*H*$_2$X (X = Cl, Br) and between H-4 and C*H*(CO$_2$Et)$_2$ were observed. Thus, the 3,4-*trans* stereochemistry of **2a**,**b** was determined.

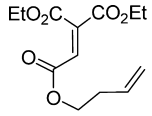


The reaction of **1** with 2 equiv of $FeCl_3$ at room temperature for 17 h gave the noncyclized H_2O-adduct **3** in 42% yield as a major product. The reaction of **1** with 2 equiv of ZnI_2 at room temperature gave **3** in 59% yield as a major product, and the reaction at 80 °C in 1,2-dichloroethane gave only starting material **1**.[11,12] The reaction of **1** with 2 equiv of $TiCl_4$ at −40 °C gave the noncyclized Cl-adduct **4** in 77% yield as a major product. Formation of compounds **3** and **4** may be reversible as they were converted to **2a** by treatment with 2 equiv of $TiCl_4$ at room temperature in 61 and 86%, respectively. Alternatively, compounds **3** and **4** may be intermediates en route to lactones **2**.



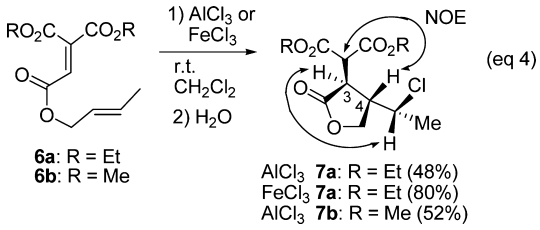
3 **4**

The reaction of 3-butenyl ester **5** with 1−2 equiv of $TiCl_4$ or $AlCl_3$ was also examined. However, the reaction gave complex mixtures. Six-membered ring formation from **5** was not an efficient process.



5

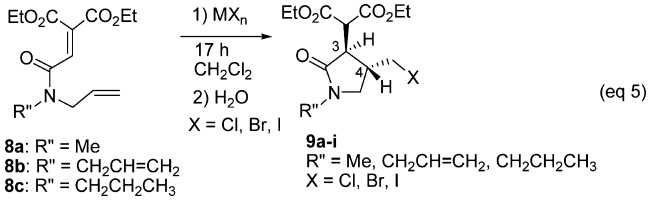
The reaction of (*E*)-2-butenyl esters **6a**,**b** with Lewis acid was next examined. The (*E*)-2-butenyl dimethyl ester **6b** is the substrate that Snider and Roush reported.[5] The reaction with 1 equiv of $AlCl_3$ or $FeCl_3$ at room temperature overnight gave diethyl 2-(4-(2-chloroethyl)tetrahydro-2-oxofuran-3-yl)malonates **7a**,**b** as major products (eq 4). The ^{1}H NMR and IR spectral data for the product **7b** are identical with the reported ones. The 3,4-*trans* stereochemistry for **7a**,**b** was suggested by NOESY



experiments. NOEs between H-3 and C*H*ClMe and between H-4 and C*H*(CO$_2$Et)$_2$ were observed. Thus, the *cis* stereochemistry of **7b** assigned in the literature is corrected to *trans*.[13]

The major products **7a** and **7b** are single diastereoisomers. The relative configuration of CHClMe to C-3, C-4 for diastereomers **7a**,**b** could be deduced as (3*S*,4*S*)-4-((*R*)-1-chloroethyl) (shown in eq 4) and (3*R*,4*R*)-4-((*S*)-1-chloroethyl) by the similar reaction mechanism for the reaction of **1** (Scheme 1, vide post). The proposed reaction mechanism for the reaction of **6** to **7** is shown in Supporting Information.

Amide substrates **8a**−**c** were then prepared by the condensation reaction of 1,1-diethyl 2-hydrogen ethenetricaboxylate (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate upon treatment with CF_3CO_2H) with the corresponding amines in the presence of HOBT, EDCI and Et_3N. Reaction of diethyl 2-((*N*-allyl-*N*-methylcarbamoyl)methylene)malonate (**8a**) with 1−2 equiv of $TiCl_4$, $FeCl_3$, $AlCl_3$, $TiBr_4$, and $AlBr_3$ at room temperature and ZnI_2 at 80 °C gave diethyl 2-(*trans*-4-(chloro(or bromo/iodo)methyl)-1-methyl-2-oxopyrrolidin-3-yl)malonate **9a**−**c** in 69−98% yields (eq 5, Table 2). Use of



2 equiv of Lewis acids such as $FeCl_3$, $AlCl_3$, and ZnI_2 increased product yields. $SnCl_4$ and $ZnBr_2$ are less effective than $TiCl_4$ and $TiBr_4$ (entries 2,3,10). Reaction of *N*,*N*-diallyl and *N*-allyl-*N*-propylcarbamoyl derivatives **8b**,**c** also gave 3,4-*trans*-pyrrolidines **9d**−**i** efficiently. The γ-lactam structures of **9a**−**i** were suggested by the presence of a characteristic C=O absorption (1688−1698 cm^{-1}). ^{1}H, ^{13}C and 2D NMR spectra were in agreement with the 5-membered ring structure. The 3,4-*trans* stereochemistry was determined by NOEs for I-adducts **9c**,**f**,**i** in $CDCl_3$ and for Cl- and Br-adducts **9a**,**b**,**d**,**e**,**g**,**h** in C_6D_6.[14,15] NOEs between H-3 and C*H*$_2$X (X = Cl, Br, I) and between H-4 and C*H*(CO$_2$Et)$_2$ were observed.

Thus, use of strong Lewis acids leads to efficient five-membered cyclization of the allyl substrates. In the cyclization, the 3,4-stereochemistry does not depend on Lewis acids.

The reaction mechanism to give the halogenated five-membered heterocycles with 3,4-*trans* stereochemistry is proposed and shown in Scheme 1. *trans* precursor **A1** and *cis* precursor **A2** in Scheme 2 may be formed from **1** and Al_2Cl_6 reversibly. The reaction may start from the precursor **A1** consisting of **1** 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 is proposed by steric reason. One molecule of Lewis acid (for example, $AlCl_3$) may work as a

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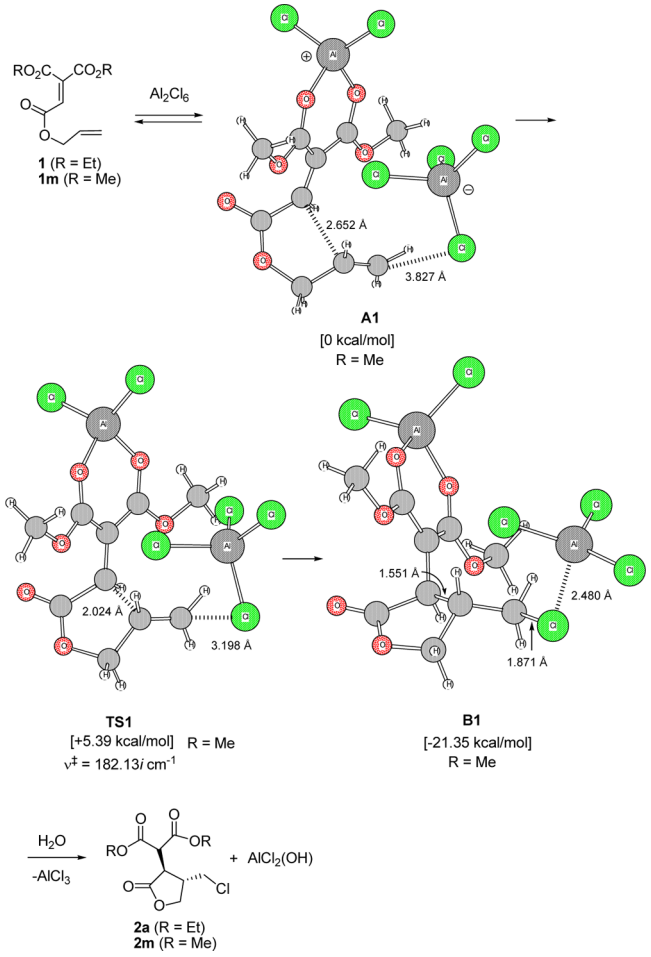
Scheme 1. Proposed Reaction Mechanism for Cyclization of Allyl Esters 1 (R = Et) and B3LYP/6-31G*-Optimized Structures and Gibbs Free Energies (T = 298.15 K and P = 1 atm) for Intermediates and TS of the Model Compounds (1m (R = Me) + Al_2Cl_6)[a]



[a]TS geometry was characterized by vibrational analysis, which checked whether the obtained geometry has single imaginary frequencies ($\nu^{\ddagger}$). From TS, reaction paths were traced by the intrinsic reaction coordinate (IRC) method to obtain the energy-minimum geometries.

catalyst and could be released after the cyclization step. Protonation and removal of $AlCl_2OH$ yield the product **2**.

In order to support this hypothesis, the structures of the intermediates and transition states (TS) of model compounds (the corresponding methyl esters and Al_2Cl_6) were calculated using B3LYP/6-31G*. $\Delta G^{\ddagger}$ for TS1 leading to 3,4-*trans*-tetrahydrofuran is found to be lower than that of TS2 leading to 3,4-*cis*-tetrahydrofuran (Scheme 2). According to the observed *trans* selectivity and preferable use of excess Lewis acids in some cases, the proposed mechanism involving Al_2Cl_6 is likely.[16] Cyclization mechanism and the stereochemistry of (*E*)-2-butenyl esters (**6** in eq 4) and allyl amides (**8** in eq 5) were also calculated by using the model compounds **6b** and the corresponding dimethyl ester of **8a** with Al_2Cl_6. These calculation results are similar to that for **1m** + Al_2Cl_6. Thus, formation of 3,4-*trans* five-membered rings are lower energy process than that of 3,4-*cis*. The results are shown in Supporting Information.

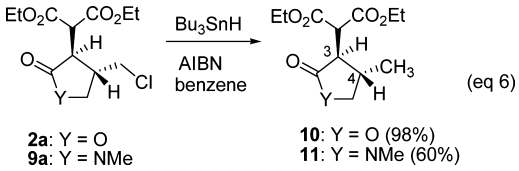
Next, reductive dechlorination of tetrahydrofuran and pyrrolidine was performed as an example of transformation of

Table 2. Reactions of Allyl Amides 8

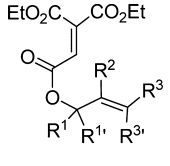
entry	R″	MX_n	MX_n (equiv)	temp (°C)		X	yield (%)
1	Me	$TiCl_4$	1	rt	**9a**	Cl	98
2	Me	$SnCl_4$	1	rt	**9a**	Cl	28
3	Me	$SnCl_4$	2	rt	**9a**	Cl	38
4	Me	$FeCl_3$	1	rt	**9a**	Cl	17
5	Me	$FeCl_3$	2	rt	**9a**	Cl	83
6	Me	$AlCl_3$	1	rt	**9a**	Cl	65[a]
7	Me	$AlCl_3$	2	rt	**9a**	Cl	76
8	Me	$AlBr_3$	1	rt	**9b**	Br	69
9	Me	$TiBr_4$	1	rt	**9b**	Br	87
10	Me	$ZnBr_2$	1	rt	**9b**	Br	47
11	Me	ZnI_2	1 × 2[b]	rt	**9c**	I	73
12	Me	ZnI_2	2	80[c]	**9c**	I	69
13	$CH_2CH{=}CH_2$	$TiCl_4$	1	rt	**9d**	Cl	86
14	$CH_2CH{=}CH_2$	$TiBr_4$	1	rt	**9e**	Br	71
15	$CH_2CH{=}CH_2$	ZnI_2	1 × 2[b]	rt	**9f**	I	59
16	$CH_2CH{=}CH_2$	ZnI_2	2	80[c]	**9f**	I	77
17	$CH_2CH_2CH_3$	$TiCl_4$	1	rt	**9g**	Cl	48[a]
18	$CH_2CH_2CH_3$	$TiCl_4$	2	rt	**9g**	Cl	98
19	$CH_2CH_2CH_3$	$FeCl_3$	2	rt	**9g**	Cl	54
20	$CH_2CH_2CH_3$	$TiBr_4$	1	rt	**9h**	Br	88
21	$CH_2CH_2CH_3$	ZnI_2	1 × 2[b]	rt	**9i**	I	67
22	$CH_2CH_2CH_3$	ZnI_2	2	80[c]	**9i**	I	87

[a]A small amount of starting material and impurity could not be removed. [b]The reaction with ZnI_2 (1 equiv) for 17 h gave the crude products including impurities (possibly noncyclized water-adducts) after workup. The crude products were further treated with ZnI_2 (1 equiv) to give the pure products **9c,f,i**. [c]In CH_2ClCH_2Cl.

the halogenated products. The reaction of **2a** or **9a** with Bu_3SnH and AIBN gave dechlorinated tetrahydrofuran **10** and pyrrolidine **11**, respectively (eq 6). The stereochemistry of **11** was determined as 3,4-*trans* by NOESY experiment.



Cyclization of Alkyl Substituted Allylic Ethenetricarboxylates. Reactions of alkyl-substituted allylic ethenetricarboxylates with Lewis acids were investigated. The alkyl substitution pattern of allylic esters have been studied for mainly $R^3/R^{3\prime}$ = Me or Ph (dimethyl esters) by Snider and Roush (eq 1) and in this study (eq 4). In order to examine the effect of alkyl substitution of $R^1/R^{1\prime}$, R^2, the reaction of substrates shown below under similar reaction conditions were carried out.



1: $R^1 = R^{1\prime} = R^2 = R^3 = R^{3\prime}$ = H
6a: $R^1 = R^{1\prime} = R^2 = R^{3\prime}$ = H; R^3 = Me
12: R^1 = Me; $R^{1\prime} = R^2 = R^3 = R^{3\prime}$ = H
14: $R^1 = R^{1\prime}$ = Me, $R^2 = R^3 = R^{3\prime}$ = H
16: $R^1 = R^{1\prime} = R^2$ = H; $R^3 = R^{3\prime}$ = Me
18: $R^1 = R^{1\prime} = R^3 = R^{3\prime}$ = H; R^2 = Me

The reaction of **12** with $AlCl_3$, $TiCl_4$ and $FeCl_3$ (1−2 equiv) at room temperature gave mixtures of 5-methyl-2-oxotetrahydrofuran **13** and *trans*-4-(1-chloroethyl)-2-oxotetrahydrofuran **7a** in ratios 1.3:1 to 0.3:1 (**13**:**7a**; eq 7). The isomeric mixture

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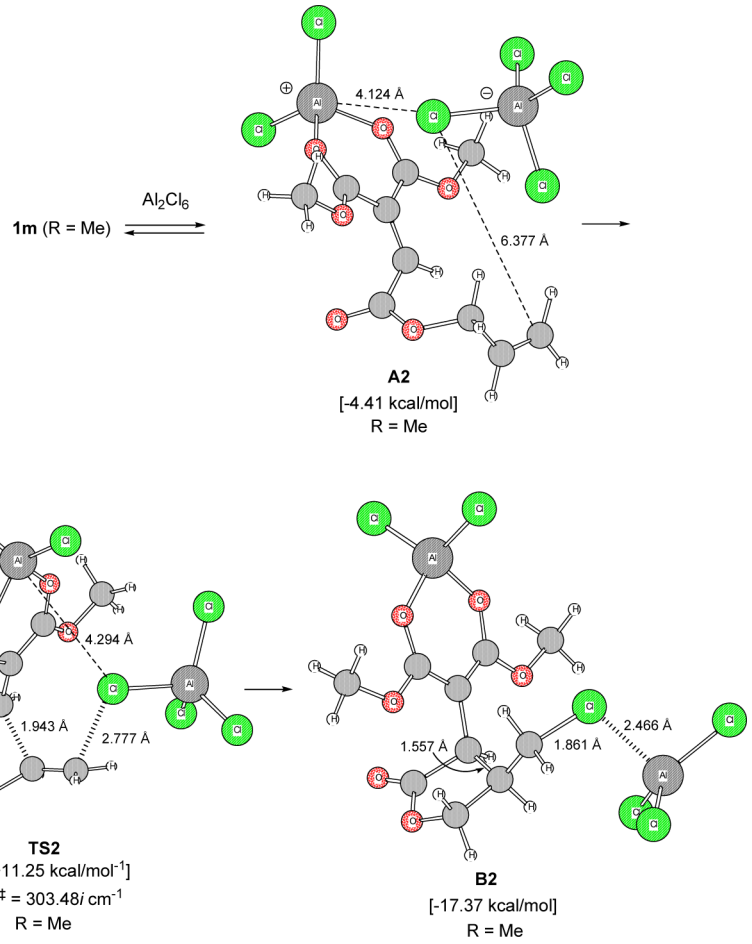
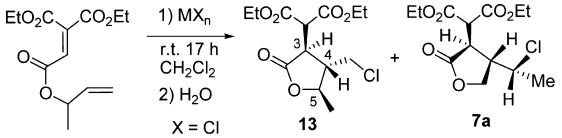
Scheme 2. Reaction Pathway Leading to 3,4-*cis* Intermediate B2 for Model Compounds (1m + Al_2Cl_6)[a]



[a]B3LYP/6-31G*-optimized structures of the model compounds are shown. The Gibbs free energies are relative to **A1** (R = Me) in Scheme 1.

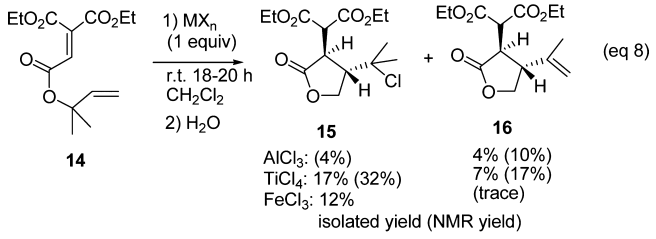
could not be separated. The compound **7a** is the product by the reaction of **6a** shown in eq 4, i.e., the structural isomer of **12**.



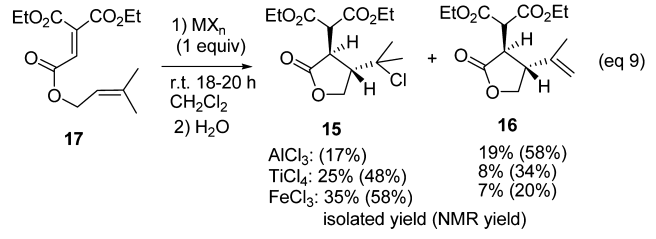
(eq 7)

$AlCl_3$ 1 equiv. **13**:**7a** = 1.3 : 1 (combined yield 52%)
$AlCl_3$ 2 equiv. **13**:**7a** = 1 : 1 (combined yield 33%)
$TiCl_4$ 1 equiv. **13**:**7a** = 1.3 : 1 (combined yield 40%)
$TiCl_4$ 2 equiv. **13**:**7a** = 1.3 : 1 (combined yield 37%)
$FeCl_3$ 1 equiv. **13**:**7a** = 0.3 : 1 (combined yield 33%)

Similarly, the reaction of **14** with $AlCl_3$, $TiCl_4$ and $FeCl_3$ (1 equiv) at room temperature overnight gave 4-*trans*-(2-chloro-2-propanyl)-2-oxotetrahydrofuran **15** in low yields, along with 2-propenyl derivative **16** (eq 8). The compound **15** and the ene product **16** were also obtained by the reaction of **17** (eq 9). The reaction of **17** is similar to that of the corresponding methyl ester that Snider and Roush reported.[5] The stereochemistry of the products **15** and **16** were determined as 3,4-*trans* by NOESY spectra.[17]



(eq 8)



(eq 9)

Formation of **7a** from **12** and **15** from **14** may be explained as follows. Secondary or tertiary allylic cation intermediate **I** may be formed by Lewis acid in situ. The isomerization of the ester **12** to **6a** and the ester **14** to **17** may lead to cyclization of **6a** to **7a** and **17** to **15** (Scheme 3). The substrate **14** rearranges to **17** via the stable tertiary allylic cation **I** (R^1 = $R^{1\prime}$ = Me) prior to cyclization of **14**. The substrate **17** may be thermodynamically more stable than **14**, because of the more substituted alkenyl group.

Related Lewis acid-catalyzed C−O scission and subsequent cycloaddition of 2-tertiary alkyl ester of ethenetricarboxylate has been reported previously.[18] B3LYP3/6-31G* optimized structure of model compound **14m** (for ethenetricarboxylate **14**) with $AlCl_3$ coordinated at 2-ester oxygen has longer C−O

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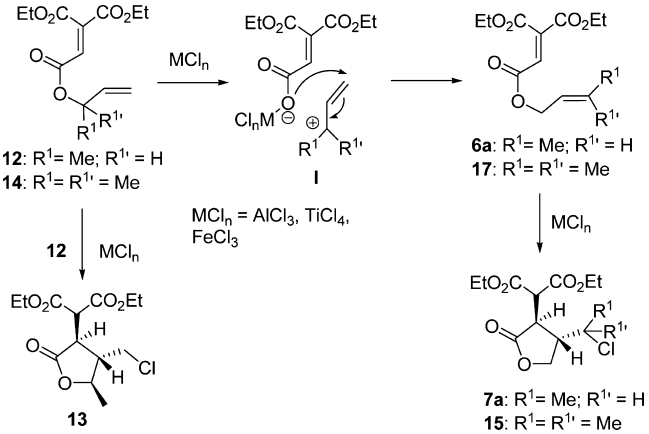
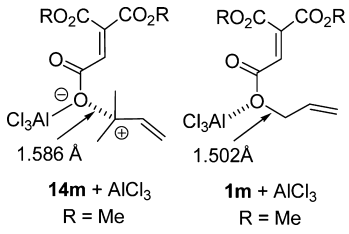
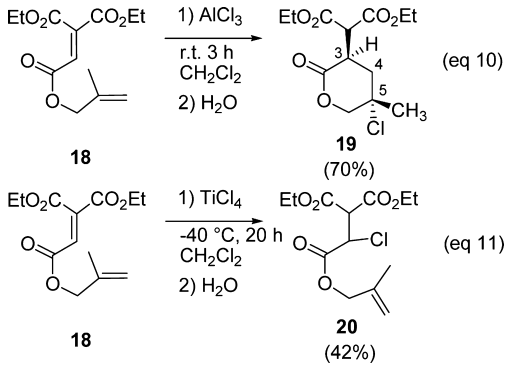
Scheme 3. Proposed Mechanism for Formation of 7a from 12 and 15 from 14



distance (1.586 Å) than that of **1m** + $AlCl_3$ (1.502 Å), which shows the ion pair character of **14m** + $AlCl_3$.



Interestingly, the reaction of **18** with $AlCl_3$ (1 equiv) gave 5-chloro-5-methyl-2-oxotetrahydro-2*H*-pyran **19** as an isolable major product (eq 10). The δ-lactam structure of **19** was



suggested by the observed C=O absorptions (1738 cm^{-1} together with ethyl esters). ^1H, ^{13}C and 2D NMR spectra were in agreement with the six-membered ring structure. Assuming the stable C-3 equatorial ($CH(CO_2Et)_2$) conformation and the absence of NOE peaks between H-3 (axial) and 5-CH_3 suggest the stereochemistry of **19** as shown in eq 10. Use of $FeCl_3$ or $TiCl_4$ also gave compound **19** in lower yield with a complex mixture. The reaction of **18** with $TiCl_4$ (1 equiv) at −40 °C for 20 h gave the noncyclized Cl-adduct **20** in 42% yield as a major product (eq 11), similar to the reaction of **1**. Treatment of **19** with $AlCl_3$ (1 equiv) at room temperature gave **20** in 50% yield.

Formation of **19** could be considered as follows (Scheme 4). The first cyclization to give the five-membered ring intermediate **B3** may occur by kinetically favored process, similar to Scheme 1. Alkyl group migration of **B3** may lead to the stable tertiary cation six-membered ring intermediate **C3**. The attack of chloride ion from anti and syn sides of the malonate on the carbocation **C3** may be reversible. The observed diastereoselectivity of compound **19** may arise from the stable 1,3-diequatorial ($CH(CO_2Et_2)_2$ (on C-3) and larger CH_3 (on C-5)) of the six-membered ring with smaller chlorine atom (on C-5) in the axial position. Thus, the attack of chloride ion to **C3** from anti-side of the malonate gives intermediate **D3** (path a).

Alternatively, intramolecular reaction of alkene moiety gives the stable tertiary cation six-membered ring intermediate **C3** (path b), followed by Cl^- attack leading to **D3**. Or, six-membered formation along with attack of Cl^- may lead to intermediate **D3** from **A3** directly (path c). Dyotropic rearrangement of the five-membered intermediate **B3** to six-membered ring intermediate **D3** (path d) is also possible.[19]

The reaction paths were examined using model compounds (the corresponding methyl esters and Al_2Cl_6). Only path a has been obtained by the model calculations.[20,21] The TS energies of TS4 and TS5 are lower than the five-membered ring formation TS3. Six-membered ring intermediate **D3** may form intermediate **D′3** by removal of catalytic $AlCl_3$. Intermediate **D′3** is slightly more stable than the five-membered intermediate **B′3**, which may be formed from **B3**. Protonation of the intermediate **D′3** yields the product **19**. The six-membered diastereomers, **E3** and **E′3**, which may be formed reversibly, are thermodynamically less stable than **D3** and **D′3**, respectively, as discussed above. Further synthetic application and detailed mechanistic study for the six-membered ring formation are under investigation. Thus, for some alkyl-substituted substrates, cationic intermediates may be formed under the reaction conditions, and rearranged products have been obtained.[22]

In summary, a Lewis acid-promoted reaction of alkenyl ethenetricarboxylates and the corresponding amides to give 3,4-*trans*-halogenomethyl 2-oxotetrahydrofuran and pyrrolidine derivatives has been found. The reaction proceeds stereoselectively. Strong Lewis acids such as $TiCl_4$ and $AlCl_3$ work efficiently. The highly functionalized and halogenated five-membered heterocyclic compounds generated in this reaction should be useful synthetic intermediates. Studies of the detailed reaction mechanism and transformations of the functionalized cyclic compounds are under investigation.

EXPERIMENTAL SECTION

General Methods. ^1H 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.

Ethenetricarboxylate **1** was prepared according to the literature.[10a] **6b** was prepared according to the literature.[23]

Ethenetricarboxylates **5**, **6a**, **12**, **14**, **15**, **17** and **18** were prepared by the reaction of diethyl ketomalonate with the corresponding (triphenylphosphoranylidne)acetate according to the literature procedure.[10a,17] These (triphenylphosphoranylidne)acetate esters were prepared by the corresponding chloroacetates and triphenylphosphine in benezene and subsequent treatment with NaOH. The chloroacetates were preprared by the reaction of the corresponding alcohols (1 equiv) and chloroacetyl chloride (1 equiv) in the presence of pyridine (1 equiv) in ether at 0 °C. Data of the ethenetricarboxylates and chloroacetates for new (triphenylphosphoranylidne)acetate esters are shown below.

3-Butenyl 2-chloroacetate. (69.3 mmol scale, 9.14 g, 89%); colorless oil: bp 81−82 °C/4.2 mmHg; ^1H NMR (400 MHz, $CDCl_3$)

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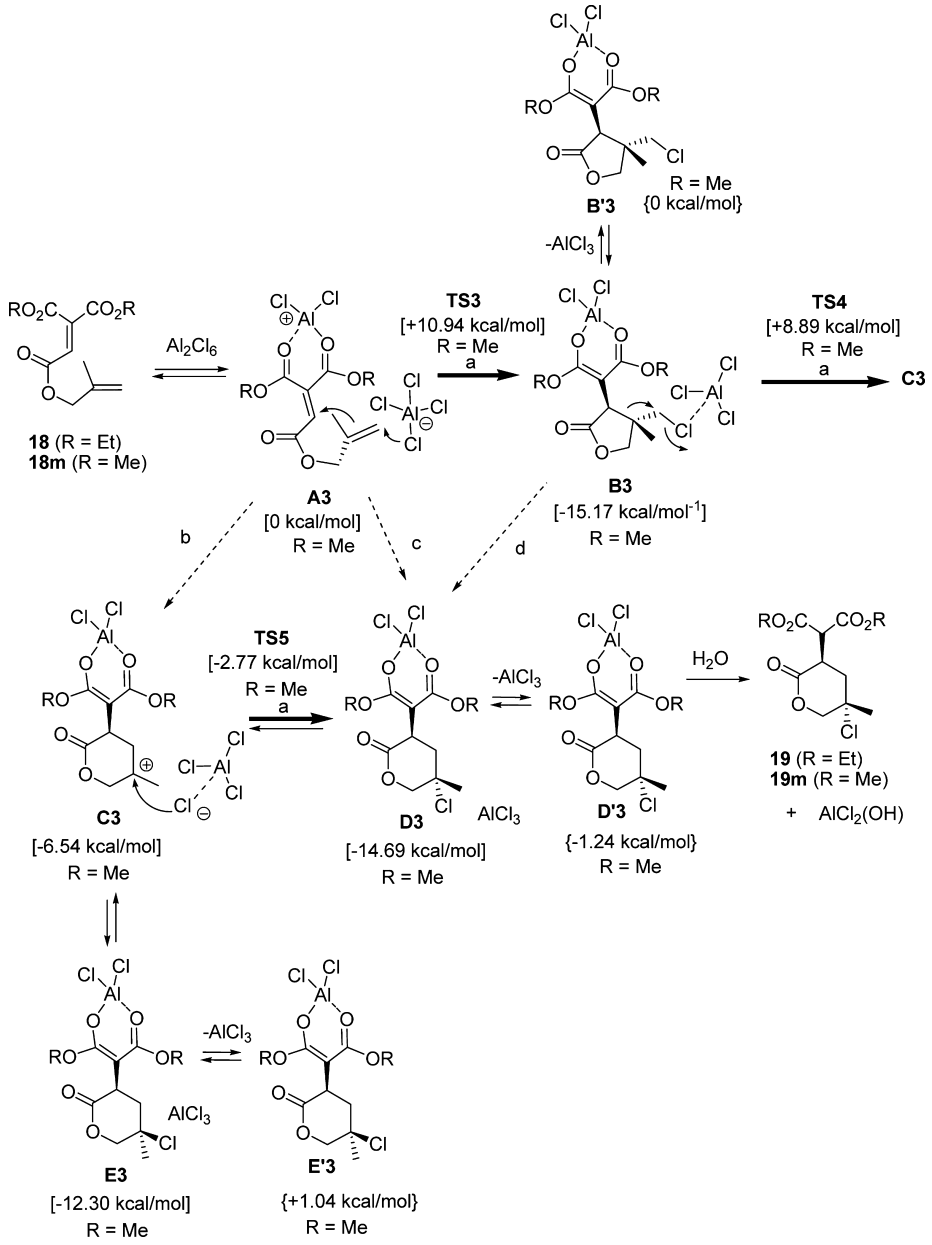
Scheme 4. Proposed Mechanism for Formation of 19 from 18[a]



[a]Proposed reaction mechanism for cyclization of **18** (R = Et) and model compound **18m** (R = Me) with Al_2Cl_6 and the B3LYP/6-31G* calculated Gibbs free energies (T = 298.15 K and P = 1 atm) for intermediates and TS of the model compounds (**18m** + Al_2Cl_6). The B3LYP/6-31G* calculated Gibbs free energies { } for **B′3**, **D′3** and **E′3** are relative to **B′3**.

δ (ppm) 2.43 (tddd, J = 6.8, 6.8, 1.4, 1.4 Hz, 2H), 4.07 (s, 2H), 4.25 (t, J = 6.8 Hz, 2H), 5.10 (ddt, J = 10.3, 1.6, 1.3 Hz, 1H), 5.13 (ddt, J = 17.0, 1.6, 1.6 Hz, 1H), 5.78 (ddt, J = 17.0, 10.3, 6.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 32.9 (t), 40.9 (t), 65.2 (t), 117.7 (t), 133.4 (d), 167.4 (s); IR (neat) 3081, 2962, 1759, 1643, 1415, 1313, 1290, 1183, 989, 922 cm^{-1}; MS (CI) m/z 151 ([M + 1]$^+$, 35), 149 ([M + 1]$^+$, 100%); HRMS [M + 1]$^+$ 149.0372, 151.0337 (calcd for $C_6H_{10}ClO_2$ [M + 1]$^+$ 149.0369, 151.0340). Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11. Found: C, 48.57; H, 6.20.

1-(3-Butenyl) 2,2-diethyl ethene-1,2,2-tricarboxylate (5). (16.3 mmol scale, 2.88 g, 65%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.43 (tddd, J = 6.8, 6.8, 1.4, 1.4 Hz, 2H), 4.24 (t, J = 6.8 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 5.10 (ddt, J = 10.3, 1.6, 1.1 Hz, 1H), 5.13 (ddt, J = 17.0, 1.6, 1.6 Hz, 1H), 5.78 (ddt, J = 17.0, 10.3, 6.8 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (q), 14.0 (q), 32.8 (t), 62.1 (t), 62.5 (t), 64.8 (t), 117.7 (t), 129.9 (d), 133.4 (d), 139.1 (s), 162.3 (s), 163.6 (s), 164.3 (s); IR (neat) 2984, 1726, 1644, 1467, 1373, 1346, 1258, 1182, 1067, 1024 cm^{-1}; MS (CI) m/z 271 ([M + 1]$^+$); HRMS 271.1187 (calcd for $C_{13}H_{19}O_6$ [M + 1]$^+$ 271.1182). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.60; H, 6.90.

1-((*E*)-2-Butenyl) 2,2-diethyl ethene-1,2,2-tricarboxylate (6a). (15 mmol scale, 2.90 g, 72%); colorless 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), 1.73 (bd, J = 6.4 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.61 (d-like, J = 6.6 Hz, 2H), 5.59 (dtq, J = 15.0, 6.6, 1.6 Hz, 1H), 5.83 (dqt, J = 15.1, 6.4, 1.1 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (q), 14.01 (q), 17.8 (q), 62.1 (t), 62.5 (t), 66.5 (t), 124.2 (d), 130.0 (d), 132.7 (d), 139.1 (s), 162.3 (s), 163.4 (s), 164.3 (s); IR (neat) 2984, 1726, 1650, 1447, 1372, 1345, 1257, 1179, 1067, 1022, 969 cm^{-1}; MS (CI) m/z 271 ([M + 1]$^+$);

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HRMS $[M + 1]^+$ 271.1180 (calcd for $C_{13}H_{19}O_6$ $[M + 1]^+$ 271.1182). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.70; H, 6.82.

3-Buten-2-yl 2-chloroacetate. (30.4 mmol scale, 4.25 g, 94%); colorless oil: bp 65−66 °C/4.2 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.37 (d, J = 6.6 Hz, 3H), 4.06 (s, 2H), 5.19 (ddd, J = 10.4, 1.2, 1.2 Hz, 1H), 5.30 (ddd, J = 17.2, 1.2, 1.2 Hz, 1H), 5.42 (qddd, J = 6.6, 6.0, 1.2, 1.2 Hz, 1H), 5.85 (ddd, J = 17.2, 10.4, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 19.8 (q), 41.1 (t), 73.2 (d), 116.8 (t), 136.7 (d), 166.5 (s); IR (neat) 3091, 2987, 1753, 1647, 1452, 1414, 1288, 1187, 1138, 1044, 992, 953 cm^{-1}; MS (CI) m/z 151 ($[M + 1]^+$, 30), 149 ($[M + 1]^+$, 100%); HRMS $[M + 1]^+$ 149.0358, 151.0307 (calcd for $C_6H_{10}ClO_2$ $[M + 1]^+$ 149.0369, 151.0340). Anal. Calcd for $C_6H_9ClO_2$: C, 48.50; H, 6.11. Found: C, 48.42; H, 6.21.

1-(3-Buten-2-yl) 2,2-diethyl ethene-1,2,2-tricarboxylate (12). (18.2 mmol scale, 3.07 g, 62%); colorless 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), 1.36 (d, J = 6.4 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 5.18 (ddd, J = 10.6, 1.2, 1.2 Hz, 1H), 5.28 (ddd, J = 17.2, 1.2, 1.2 Hz, 1H), 5.43 (qddd, J = 6.4, 6.0, 1.2, 1.2 Hz, 1H), 5.84 (ddd, J = 17.2, 10.6, 6.0, 1H), 6.87 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) $\delta\delta$ (ppm) 13.96 (q), 14.03 (q), 19.8 (q), 62.1 (t), 62.5 (t), 72.8 (d), 116.8 (t), 130.3 (d), 136.7 (d), 138.9 (s), 162.4 (s), 162.8 (s), 164.3 (s); IR (neat) 2983, 1735, 1725, 1647, 1448, 1375, 1260, 1184, 1066 cm^{-1}; MS (CI) m/z 271 ($[M + 1]^+$); HRMS $[M + 1]^+$ 271.1189 (calcd for $C_{13}H_{19}O_6$ $[M + 1]^+$ 271.1182). Anal. Calcd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71. Found: C, 57.52; H, 6.78.

2-Methyl-3-buten-2-yl 2-chloroacetate. (30.4 mmol scale, 3.73 g, 75%); colorless oil: bp 95−105 °C/53 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.57 (s, 6H), 3.99 (s, 2H), 5.13 (dd, J = 10.9, 0.6 Hz, 1H), 5.23 (dd, J = 17.5, 0.6 Hz, 1H), 6.08 (dd, J = 17.5, 10.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 26.3 (q), 41.9 (t), 83.3 (s), 113.8 (t), 141.5 (d), 166.0 (s); IR (neat) 2985, 1754, 1414, 1382, 1367, 1314, 1199, 1123 cm^{-1}; MS (EI) m/z 165 ($[M + 1]^+$, 39), 163 ($[M + 1]^+$, 100%); HRMS $[M + 1]^+$ 163.0527 (calcd for $C_7H_{12}ClO_2$ $[M + 1]^+$ 163.0526), M^+ 162.0452 (calcd for $C_7H_{11}ClO_2$ M^+ 162.0448).

1,1-Diethyl 2-(2-methyl-3-buten-2-yl) ethene-1,1,2-tricarboxylate (14). (11.8 mmol scale, 1.39 g, 41%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) $\delta\delta$ (ppm) 1.31 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.56 (s, 6H), 4.29 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7.1 Hz, 2H), 5.12 (dd, J = 10.9, 0.7 Hz, 1H), 5.21 (dd, J = 17.4, 0.5 Hz, 1H), 6.08 (dd, J = 17.4, 10.9 Hz, 1H), 6.82 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.96 (q), 14.04 (q), 26.3 (q), 62.0 (t), 62.4 (t), 83.1 (s), 113.7 (t), 131.8 (d), 137.9 (s), 141.5 (d), 162.4 (s), 162.6 (s), 164.3 (s); IR (neat) 2984, 1725−1742, 1645, 1468, 1447, 1376, 1349, 1265, 1188, 1126, 1066, 1023 cm^{-1}; MS (Ei) m/z 284 (M^+, 0.4), 200 (42), 154 (68), 143 (80), 69 (100%); HRMS M^+ 284.1261 (calcd for $C_{14}H_{20}O_6$ M^+ 284.1260).

1,1-Diethyl 2-(3-methylbut-2-enyl) ethene-1,1,2-tricarboxylate (17). (14.9 mmol scale, 2.32 g, 55%); 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), 1.72 (narrow multiplet, 3H), 1.77 (narrow multiplet, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.68 (bd, J = 7.5 Hz, 2H), 5.35 (tqq, J = 7.5, 1.4, 1.4 Hz, 1H), 6.87 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (q), 14.0 (q), 18.1 (q), 25.8 (q), 62.1 (t), 62.5 (t), 62.6 (t), 117.6 (d), 130.2 (d), 138.9 (s), 140.5 (s), 162.4 (s), 163.6 (s), 164.4 (s); IR (neat) 2983, 1725, 1648, 1466, 1447, 1377, 1348, 1258, 1178, 1066, 1022 cm^{-1}; MS (EI) m/z 284 (M^+, 14), 238 (43), 217 (100%); HRMS M^+ 284.1264 (calcd for $C_{14}H_{20}O_6$ M^+ 284.1260).

2-Methyl-2-propenyl 2-chloroacetate. (30.4 mmol scale, 4.30 g, 95%); colorless oil: bp 60−70 °C/5.1 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.78 (narrow multiplet, 3H), 4.11 (s, 2H), 4.61 (bs, 2H), 4.98 (narrow multiplet, 1H), 5.02 (narrow multiplet, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 19.4 (q), 40.8 (d), 69.3 (d), 113.9 (d), 139.1 (s), 167.0 (s); IR (neat) 3085, 2951, 1762, 1660, 1452, 1413, 1312, 1171, 1031, 998 cm^{-1}; MS (EI) m/z 150 (M^+, 4.8), 148 (M^+, 14), 77 (36), 72 (100%); HRMS M^+ 148.0291, 150.0263 (calcd for $C_6H_9ClO_2$ M^+ 148.0291, 150.0262).

1,1-Diethyl 2-(2-methyl-2-propenyl) ethene-1,1,2-tricarboxylate (18). (16 mmol scale, 3.47 g, 80%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.33 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.77 (bs, 3H), 4.31 (q, J = 7.1 Hz, 2H), 4.36 (q, J = 7.1 Hz, 2H), 4.61 (s, 2H), 4.97 (qt, J = 0.7, 0.7 Hz, 1H), 5.01 (bs, 1H), 6.91 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (q), 14.0 (q), 19.5 (q), 62.2 (t), 62.6 (t), 69.1 (t), 114.1 (t), 129.8 (d), 139.0 (s), 139.3 (s), 162.3 (s), 163.3 (s), 164.3 (s); IR (neat) 2984, 1728, 1656, 1447, 1375, 1345, 1258, 1179, 1067, 1022 cm^{-1}; MS (CI) m/z 271 ($[M + 1]^+$); HRMS $[M + 1]^+$ 271.1176 (calcd for $C_{13}H_{19}O_6$ $[M + 1]^+$ 271.1182).

Typical Experimental Procedure (eq 3, Table 1, entry 6). To a solution of **1** (128 mg, 0.5 mmol) in CH_2Cl_2 (2 mL) was $TiCl_4$ (190 mg, 110 μL, 0.1 mmol). The mixture was stirred at room temperature for 17 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 to give **2a** (134 mg, 90%).

Diethyl 2-(*trans*-4-(chloromethyl)-2-oxotetrahydrofuran-3-yl)malonate (2a). Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 3.09 (dd, J = 8.4, 4.1, 1H), 3.20 (ddddd, J = 8.7, 8.4, 7.1, 6.2, 4.0 Hz, 1H), 3.66 (dd, J = 11.4, 6.2 Hz, 1H), 3.72 (dd, J = 11.4, 4.0 Hz, 1H), 4.06 (d, J = 4.1 Hz, 1H), 4.20 (dd, J = 9.2, 7.1 Hz, 1H), 4.21−4.33 (m, 4H), 4.55 (dd, J = 9.2, 8.7 Hz, 1H); Selected NOEs are between δ 3.09 (H-3) and δ 3.66, 3.72 (CH_2Cl) and between δ 3.20 (H-4) and δ 4.06 ($CH(CO_2Et)_2$), 4.55 (H-5b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.97 (q), 14.01 (q), 39.3 (d), 42.0 (d), 45.5 (t), 50.9 (d), 62.31 (t), 62.32 (t), 69.5 (t), 167.3 (s), 167.8 (s), 175.8 (s); Selected HMBC correlations are between δ 3.09 (H-3) and δ 45.5 (CH_2Cl), 50.9 $CH(CO_2Et)_2$), 39.3 (C-4), between δ 3.20 (H-4) and δ 42.0 (C-3), and between δ 4.20, 4.55 (H-5a,5b) and δ 45.5 (CH_2Cl), 39.3 (C-4); IR (neat) 2984, 1777, 1734, 1446, 1393, 1373, 1256, 1183, 1096, 1028 cm^{-1}; MS (EI) m/z 294 (M^+, 36%), 292 (M^+, 100%); HRMS M^+ 292.0720, 294.0706 (calcd for $C_{12}H_{17}ClO_6$ 292.0714, 294.0684).

Diethyl 2-(*trans*-4-(bromomethyl)-2-oxotetrahydrofuran-3-yl)malonate (2b). (Table 1, entry 3, 1 mmol scale, 193 mg, 57%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 3.07 (dd, J = 8.6, 4.2, 1H), 3.17 (ddddd, J = 8.6, 8.5, 7.3, 6.8, 3.8 Hz, 1H), 3.51 (dd, J = 10.6, 6.8 Hz, 1H), 3.60 (dd, J = 10.6, 3.8 Hz, 1H), 4.05 (d, J = 4.0 Hz, 1H), 4.15 (dd, J = 9.3, 7.3 Hz, 1H), 4.20−4.33 (m, 4H), 4.54 (dd, J = 9.3, 8.5 Hz, 1H); Selected NOEs are between δ 3.07 (H-3) and δ 3.51, 3.60 (CH_2Br), between δ 3.17 (H-4) and δ 4.05 ($CH(CO_2Et)_2$), 4.54 (H-5b), and between δ 4.15 (H-5a) and δ 3.51, 3.60 (CH_2Br); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (q), 14.0 (q), 34.5 (t), 39.0 (d), 43.4 (d), 50.8 (d), 62.3 (t × 2), 70.6 (t), 167.2 (s), 167.7 (s), 175.7 (s); Selected HMBC correlations are between δ 3.07 (H-3) and δ 34.5 (CH_2Br), 50.8 $CH(CO_2Et)_2$), 39.0 (C-4), between δ 3.51, 3.60 (CH_2Br) and δ 43.4 (C-3), 39.0 (C-4), and between δ 4.15, 4.54 (H-5a,b) and δ 34.5 (CH_2Br), 39.0 (C-4); IR (neat) 2983, 1779, 1740, 1475, 1446, 1391, 1373, 1234, 1183, 1029 cm^{-1}; MS (EI) m/z 338 (M^+, 100%), 336 (M^+, 100%); HRMS M^+ 336.0204, 338.0175 (calcd for $C_{12}H_{17}BrO_6$ 336.0209, 338.0188).

3: (2 equiv of ZnI_2, rt, 0.5 mmol scale, 81 mg, 59%); colorless 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), 3.33 (bs, 1H), 3.96 (d, J = 4.2 Hz, 1H), 4.21−4.30 (m, 4H), 4.699 (ddd, J = 5.9, 1.3, 1.3 Hz, 1H), 4.702 (ddd, J = 5.9, 1.3, 1.3 Hz, 1H), 4.76 (d, J = 4.2 Hz, 1H), 5.27 (dddd, J = 10.4, 1.2, 1.2, 1.2 Hz, 1H), 5.35 (dddd, J = 17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.91 (dddd, J = 17.2, 10.4, 5.9, 5.9 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.00 (q), 14.04 (q), 55.2 (d), 62.0 (t), 62.1 (t), 66.7 (t), 69.7 (d), 119.3 (t), 131.3 (d), 167.0 (s), 167.2 (s), 171.5 (s); IR (neat) 3501, 2986, 1739, 1651, 1466, 1448, 1372, 1260, 1177, 1031 cm^{-1}; MS (EI) m/z 275 ($[M + 1]^+$, 14), 201 (50), 189 (100%); HRMS $[M + 1]^+$ 275.1129 (calcd for $C_{12}H_{19}O_7$ $[M + 1]^+$ 275.1131). Anal. Calcd for $C_{12}H_{18}O_7$: C, 52.55; H, 6.62. Found: C, 52.26; H, 6.80.

4: (2 equiv of $TiCl_4$, −40 °C, 0.5 mmol scale, 113 mg, 77%); compound **4** is unstable to column chromatography (SiO_2) and partial decomposition of **4** to starting material **1** was observed; colorless oil;

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^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 4.01 (d, J = 10.3 Hz, 1H), 4.17−4.31 (m, 4H), 4.700 (ddd, J = 5.8, 1.2, 1.2 Hz, 1H), 4.703 (ddd, J = 5.8, 1.2, 1.2 Hz, 1H), 4.82 (d, J = 10.3 Hz, 1H), 5.29 (dddd, J = 10.6, 1.2, 1.2, 1.2 Hz, 1H), 5.39 (dddd, J = 17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.93 (dddd, J = 17.2, 10.6, 5.8, 5.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 52.7 (d), 56.4 (d), 62.4 (t), 62.5 (t), 66.9 (t), 119.2 (t), 131.0 (d), 165.6 (s), 166.0 (s), 167.5 (s); IR (neat) 2985, 1741, 1650, 1447, 1306, 1166, 1096, 1029 cm^{-1}; MS (EI) m/z 294 (M$^+$, 36), 292 (100%); HRMS M$^+$ 292.0717, 294.0706 (calcd for $C_{12}H_{17}ClO_6$ M$^+$ 292.0714, 294.0684).

Diethyl 2-(*trans*-4-(1-chloroethyl)-2-oxotetrahydrofuran-3-yl)malonate (7a). (1 equiv of $FeCl_3$, 1.05 mmol scale, 285 mg, 80%); including a small amount of impurity, possibly containing ene adduct;[5] colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.28 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.49 (d, J = 6.8 Hz, 3H), 3.09 (dddd, J = 9.0, 8.0, 6.8, 3.1 Hz, 1H), 3.19 (dd, J = 8.0, 3.9 Hz, 1H), 4.07 (d, J = 3.9 Hz, 1H), 4.19−4.32 (m, 5H), 4.37 (dd, J = 9.2, 6.8 Hz, 1H), 4.48 (dd, J = 9.2, 9.0 Hz, 1H); Selected NOEs are between δ 3.19 (H-3) and δ 1.49 (CHCH_3Cl), 4.19−4.32 (CHCH$_3$Cl, overlapped), between δ 3.09 (H-4) and δ 4.07 (CH(CO$_2$Et)$_2$), 4.48 (H-5b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 23.0 (q), 42.4 (d), 44.1 (d), 51.0 (d), 58.7 (d), 62.30 (t), 62.33 (t), 67.1 (t), 167.5 (s), 168.0 (s), 176.1 (s); Selected HMBC correlations are between δ 3.19 (H-3) and δ 51.0 CH(CO$_2$Et)$_2$), 44.1 (C-4), between δ 3.09 (H-4) and δ 42.4 (C-3), 51.0 (CH(CO$_2$Et)$_2$), 58.7 (CHCH$_3$Cl), 67.1 (C-5), and between δ 4.37, 4.48 (H-5a,b) and δ 58.7 (CHCH$_3$Cl), 44.1 (C-4); IR (neat) 2984, 1777, 1733, 1467, 1446, 1373, 1265, 1182, 1033 cm^{-1}; MS (CI) m/z 309 ([M + 1]$^+$, 36%), 307 ([M + 1]$^+$, 100%); HRMS [M + 1]$^+$ 307.0954, 309.0949 (calcd for $C_{13}H_{20}ClO_6$ 307.0948, 309.0919).

Dimethyl 2-(*trans*-4-(1-chloroethyl)-2-oxotetrahydrofuran-3-yl)malonate (7b). (eq 4, 0.54 mmol scale, 78 mg, 52%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.50 (d, J = 6.8 Hz, 3H), 3.07 (dddd, J = 8.9, 8.1, 6.8, 3.2 Hz, 1H), 3.20 (dd, J = 8.1, 3.9 Hz, 1H), 3.78 (s, 3H), 3.82 (s, 3H), 4.11 (d, J = 3.9 Hz, 1H), 4.27 (qd, J = 6.8, 3.2 Hz, 1H), 4.36 (dd, J = 9.1, 6.8 Hz, 1H), 4.48 (dd, J = 9.1, 8.9 Hz, 1H); Selected NOEs are between δ 3.20 (H-3) and δ 1.50 (CHCH_3Cl), 4.27 (CHCH$_3$Cl), between δ 3.07 (H-4) and δ 4.11 (CH(CO$_2$Me)$_2$), 4.48 (H-5b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 23.0 (q), 42.4 (d), 44.2 (d), 50.7 (d), 53.1 (q), 53.2 (q), 58.6 (d), 67.2 (t), 167.9 (s), 168.4 (s), 175.9 (s); Selected HMBC correlations are between δ 3.20 (H-3) and δ 58.6 (CHCH$_3$Cl), 44.2 (C-4), between δ 3.07 (H-4) and δ 42.4 (C-3), and between δ 4.36, 4.48 (H-5a,b) and δ 58.6 (CHCH$_3$Cl); IR (neat) 2957, 1779, 1742, 1436, 1359, 1197, 1163, 1035 cm^{-1}; MS (EI) m/z 281 ([M + 1]$^+$, 6.9), 279 ([M + 1]$^+$, 22), 85 (93), 83 (100%); HRMS M$^+$ 278.0556 (calcd for $C_{11}H_{15}ClO_6$ 278.0557).

Preparation of Substrates 8a−c. To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (649 mg, 3 mmol) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate upon treatment with CF_3CO_2H) in THF (4.1 mL) were added *N*-allylmethylamine (0.29 mL, 213 mg, 3 mmol), Et_3N (0.42 mL, 304 mg, 3 mmol), HOBt (1-hydroxybenzotriazole) (811 mg, 6 mmol) and EDCI (1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride) (598 mg, 3.1 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, 2 M 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 (1:3) to give **8a** (718 mg, 89%).

8a: pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1.2:1) δ (ppm) 1.31 (t, J = 7.1, 3H × 0.55, major rotamer) 1.320 (t, J = 7.1 Hz, 3H × 0.45, minor rotamer), 1.323 (t, J = 7.1 Hz, 3H × 0.45), 1.33 (t, J = 7.1 Hz, 3H × 0.55), 2.98 (s, 3H × 0.55), 3.00 (s, 3H × 0.45), 3.95 (ddd, J = 5.1, 1.6, 1.6 Hz, 2H × 0.55), 4.04 (ddd, J = 6.0, 1.4, 1.4, 2H × 0.45), 4.26−4.37 (m, 4H), 5.19−5.29 (m, 2H), 5.70−5.84 (m, 1H), 7.27 (s, 1H × 0.55), 7.34 (s, 1H × 0.45); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.05 (q), 14.08 (q), 33.3 (q), 35.0 (q), 49.8 (t), 52.7 (t), 61.87 (t), 61.90 (t), 62.2 (t), 118.0 (t), 118.3 (t), 132.0 (d), 132.1 (d), 134.2 (d), 134.4 (s), 134.8 (d), 135.0 (s), 163.07 (s), 163.11 (s), 163.9 (s), 164.3 (s), 164.5 (s), 164.6 (s); IR (neat) 2986, 1734, 1657, 1468, 1448, 1408, 1375, 1257, 1069, 1023 cm^{-1}; MS (EI) m/z 269 (M$^+$, 17), 224 (36), 200 (86), 154 (100%); HRMS 269.1267 (calcd for $C_{13}H_{19}NO_5$ M$^+$ 269.1263).

8b: (3 mmol scale, 523 mg, 59%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (t, J = 7.1, 3H) 1.32 (t, J = 7.1 Hz, 3H), 3.93 (ddd, J = 5.1, 1.7, 1.7 Hz, 2H), 4.03 (ddd, J = 6.0, 1.3, 1.3 Hz, 2H), 4.29 (q, J = 7.1 Hz, 2H), 4.33 (q, J = 7.1 Hz, 2H), 5.16−5.28 (m, 4H), 5.71−5.83 (m, 2H), 7.27 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.9 (q), 14.0 (q), 47.7 (t), 49.6 (t), 61.8 (t), 62.2 (t), 117.9 (t), 118.2 (t), 132.2 (d), 132.3 (d), 134.2 (d), 135.1 (s), 163.0 (s), 164.0 (s), 164.5 (s); IR (neat) 2984, 1733, 1655, 1466, 1445, 1417, 1374, 1256, 1206, 1069 cm^{-1}; MS (EI) m/z 295 (M$^+$); HRMS 295.1422 (calcd for $C_{15}H_{21}NO_5$ M$^+$ 295.1420).

N-Allylpropylamine was prepared by reaction of propylamine with allylbromide in ethanol according to the literature procedure.[24]

8c: (3 mmol scale, 741 mg, 83%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 1:1) δ (ppm) 0.90 (t, J = 7.2, 3H × 0.5), 0.92 (t, J = 7.1 Hz, 3H × 0.5), 1.29−1.34 (m, 6H), 1.54−1.66 (m, 2H), 3.26 (dd, J = 7.6, 7.6 Hz, 2H × 0.5), 3.21−3.36 (m, 2H × 0.5), 3.94 (ddd, J = 4.9, 1.6, 1.6 Hz, 2H × 0.5), 4.03 (ddd, J = 6.0, 1.4, 1.4 Hz, 2H × 0.5), 4.26−4.36 (m, 4H), 5.16−5.27 (m, 2H), 5.72−5.85 (m, 1H), 7.26 (s, 1H × 0.5), 7.34 (s, 1H × 0.5); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.2 (q), 11.4 (q), 14.0 (q), 14.1 (q), 20.7 (t), 22.2 (t), 47.6 (t), 47.9 (t), 49.4 (t), 50.7 (t), 61.9 (t), 62.17 (t), 62.23 (t), 117.7 (t), 117.8 (t), 132.6 (d), 132.7 (d), 134.2 (d), 134.6 (d), 134.7 (s), 135.0 (s), 163.1 (s), 163.2 (s), 163.7 (s), 164.1 (s), 164.7 (s); IR (neat) 2984, 1731, 1650, 1466, 1375, 1257, 1212, 1069 cm^{-1}; MS (EI) m/z 297 (M$^+$, 0.5), 273 (4.7), 257 (70), 227 (75), 183 (74), 160 (100%); HRMS 297.1576 (calcd for $C_{15}H_{23}NO_5$ M$^+$ 297.1576).

Typical Experimental Procedure (eq 5, Table 2, entry 1). To a solution of **8a** (135 mg, 0.5 mmol) in CH_2Cl_2 (1 mL) was $TiCl_4$ (95 mg, 55 μL, 0.5 mmol). The mixture was stirred at room temperature for 17 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 (1:4) as eluent to give **9a** (150 mg, 98%).

Diethyl 2-(*trans*-4-(chloromethyl)-1-methyl-2-oxopyrrolidin-3-yl)malonate (9a). Colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.87 (s, 3H), 2.89−2.99 (m, 2H), 3.29 (dd, J = 9.8, 5.2 Hz, 1H), 3.56 (dd, J = 9.8, 9.8 Hz, 1H), 3.58 (dd, J = 11.0, 6.8 Hz, 1H), 3.72 (dd, J = 11.0, 3.9 Hz, 1H), 4.05 (d, J = 4.0 Hz, 1H), 4.13−4.30 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 29.9 (q), 36.1 (d), 44.8 (d), 47.5 (t), 51.3 (d), 51.7 (t), 61.8 (t), 61.9 (t), 167.9 (s), 168.6 (s), 172.2 (s); Selected HMBC correlations are between δ 4.05 (CH(CO$_2$Et)$_2$) and δ 44.8 (C-3), 36.1 (C-4), between δ 3.58, 3.72 (CH_2Cl) and δ 36.1 (C-4), 44.8 (C-3), and between δ 3.29, 3.56 (H-5) and δ 47.5 (CH$_2$Cl), 36.1 (C-4); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.863 (t, J = 7.1 Hz, 3H), 0.912 (t, J = 7.1 Hz, 3H), 2.45 (d, J = 0.7 Hz, 3H), 2.59 (dd, J = 9.6, 5.8 Hz, 1H), 2.73 (dd, J = 7.5, 4.5 Hz, 1H), 2.85 (ddddd, J = 9.1, 8.2, 7.5, 5.8, 3.8 Hz, 1H), 2.96 (dd, J = 10.1, 8.2 Hz, 1H), 3.00 (dd, J = 9.6, 9.1 Hz, 1H), 3.26 (dd, J = 10.1, 3.8 Hz, 1H), 3.80−3.97 (m, 4H), 4.21 (d, J = 4.5 Hz, 1H); Selected NOEs are between δ 2.73 (H-3) and δ 2.96, 3.26 (CH_2Cl) and between δ 2.85 (H-4) and δ 4.21 (CH(CO$_2$Et)$_2$); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (q), 13.9 (q), 29.3 (q), 36.3 (d), 36.8 (t), 46.3 (d), 51.6 (d), 52.4 (t), 61.5 (t), 61.6 (t), 168.0 (s), 168.7 (s), 171.6 (s); IR (neat) 2986, 2942, 1738, 1688, 1504, 1448, 1375, 1272, 1178, 1100, 1033 cm^{-1}; MS (EI) m/z 307 (M$^+$, 29), 305 (M$^+$, 80), 260 (43), 256 (100%); HRMS M$^+$ 305.1037, 307.1010 (calcd for $C_{13}H_{20}ClNO_5$ 305.1030, 307.1001).

Diethyl 2-(*trans*-4-(bromomethyl)-1-methyl-2-oxopyrrolidin-3-yl)malonate (9b). (Table 2, entry 8, 0.5 mmol scale, 121 mg, 69%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26

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(t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.88 (s, 3H), 2.87−2.98 (m, 2H), 3.26 (dd, J = 9.9, 5.4 Hz, 1H), 3.45 (dd, J = 10.3, 7.3 Hz, 1H), 3.57 (dd, J = 9.9, 8.9 Hz, 1H), 3.61 (dd, J = 10.3, 3.8 Hz, 1H), 4.05 (d, J = 4.0 Hz, 1H), 4.15−4.29 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.08 (q), 14.12 (q), 29.9 (q), 35.9 (d), 37.0 (t), 46.2 (d), 51.3 (d), 52.9 (t), 61.9 (t), 62.0 (t), 167.9 (s), 168.7 (s), 172.2 (s); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.857 (t, J = 7.1 Hz, 3H), 0.910 (t, J = 7.1 Hz, 3H), 2.45 (d, J = 0.7 Hz, 3H), 2.61 (dd, J = 9.9, 5.9 Hz, 1H), 2.74 (dd, J = 7.3, 4.7 Hz, 1H), 2.86 (ddddd, J = 9.2, 8.2, 7.3, 5.9, 3.8 Hz, 1H), 2.99 (dd, J = 10.1, 8.2 Hz, 1H), 3.02 (dd, J = 9.9, 9.2 Hz, 1H), 3.28 (dd, J = 10.1, 3.8 Hz, 1H), 3.80−3.97 (m, 4H), 4.22 (d, J = 4.7 Hz, 1H); Selected NOEs are between δ 2.74 (H-3) and δ 2.99, 3.28 (CH_2Br) and between δ 2.86 (H-4) and δ 4.22 ($CH(CO_2Et)_2$); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.8 (q), 13.9 (q), 29.3 (q), 36.4 (d), 36.9 (t), 46.4 (d), 51.7 (d), 52.4 (t), 61.5 (t), 61.6 (t), 168.1 (s), 168.7 (s), 171.5 (s); Selected HMBC correlations are between δ 2.74 (H-3) and δ 51.7 ($CH(CO_2Et)_2$), 36.4 (C-4), between δ 2.61, 3.02 (H-5) and δ 36.9 (CH_2Br), between δ 4.22 ($CH(CO_2Et)_2$) and δ 46.4 (C-3), 36.4 (C-4), and between δ 2.99, 3.28 (CH_2Br) and δ 52.4 (C-5), 46.4 (C-3); IR (neat) 2984, 2940, 1734, 1698, 1502, 1446, 1373, 1270, 1178, 1035 cm^{-1}; MS (EI) m/z 351 (M^+, 70), 349 (M^+, 70), 306 (36), 304 (28), 270 (51), 256 (100%); HRMS M^+ 349.0516, 351.0496 (calcd for $C_{13}H_{20}BrNO_5$ 349.0525, 351.0504).

Diethyl 2-(*trans*-4-(iodomethyl)-1-methyl-2-oxopyrrolidin-3-yl)malonate (9c). (Table 2, entry 11, 0.5 mmol scale, 145 mg, 73%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.71 (ddddd, J = 8.8, 8.1, 7.2, 5.8, 3.7 Hz, 1H), 2.79 (dd, J = 7.2, 4.4 Hz, 1H), 2.84 (d, J = 0.7 Hz, 3H), 3.12 (dd, J = 9.8, 5.8 Hz, 1H), 3.22 (dd, J = 10.1, 8.1 Hz, 1H), 3.43 (dd, J = 10.1, 3.7 Hz, 1H), 3.55 (dd, J = 9.8, 8.8 Hz, 1H), 4.03 (d, J = 4.4 Hz, 1H), 4.13−4.31 (m, 4H); Selected NOEs are between δ 2.79 (H-3) and δ 3.22, 3.43 (CH_2I) and between δ 2.71 (H-4) and δ 4.03 ($CH(CO_2Et)_2$), 3.55 (H-5b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.7 (t), 14.07 (q), 14.13 (q), 29.9 (q), 35.9 (d), 48.3 (d), 51.1 (d), 55.1 (t), 61.8 (t), 62.0 (t), 167.9 (s), 168.6 (s), 172.4 (s); Selected HMBC correlations are between δ 2.79 (H-3) and δ 51.13 ($CH(CO_2Et)_2$), 35.9 (C-4), 11.7 (CH_2I), between δ 3.12, 3.55 (H-5a,b) and δ 35.9 (C-4), 11.7 (CH_2I), between δ 4.03 ($CH(CO_2Et)_2$) and δ 48.3 (C-3), 35.9 (C-4), and between δ 3.22, 3.43 (CH_2I) and δ 55.1 (C-5), 35.9 (C-4), 48.3 (C-3); IR (neat) 2980, 2935, 1730, 1694, 1499, 1443, 1372, 1300, 1267, 1176, 1032 cm^{-1}; MS (EI) m/z 397 (M^+, 10), 352 (59), 306 (56), 270 (100%); HRMS M^+ 397.0381 (calcd for $C_{13}H_{20}INO_5$ 397.0386).

Diethyl 2-(*trans*-1-allyl-4-(chloromethyl)-2-oxopyrrolidin-3-yl)malonate (9d). (Table 2, entry 13, 0.5 mmol scale, 143 mg, 86%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.92−2.94 (m, 2H), 3.25 (dd, J = 9.8, 5.6 Hz, 1H), 3.55 (dd, J = 9.8, 9.6 Hz, 1H), 3.59 (dd, J = 11.2, 6.6 Hz, 1H), 3.72 (dd, J = 11.2, 3.7 Hz, 1H), 3.90 (dddd, J = 15.2, 6.0, 1.5, 1.5 Hz, 1H), 3.93 (dddd, J = 15.2, 6.0, 1.5, 1.5 Hz, 1H), 4.07 (d, J = 3.8 Hz, 1H), 4.14−4.30 (m, 4H), 5.22 (dddd, J = 10.3, 1.5, 1.5, 1.5 Hz, 1H), 5.24 (dddd, J = 17.0, 1.5, 1.5, 1.5 Hz, 1H), 5.73 (dddd, J = 17.0, 10.3, 6.0, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 36.0 (d), 45.0 (d), 45.3 (t), 47.5 (t), 49.1 (t), 51.3 (d), 61.8 (t), 61.9 (t), 118.3 (t), 131.9 (d), 167.9 (s), 168.6 (s), 171.9 (s); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.869 (t, J = 7.1 Hz, 3H), 0.907 (t, J = 7.1 Hz, 3H), 2.79 (dd, J = 9.5, 5.7 Hz, 1H), 2.86 (dd, J = 7.4, 4.3 Hz, 1H), 2.91 (ddddd, J = 9.0, 7.6, 7.4, 5.7, 3.8 Hz, 1H), 3.19 (dd, J = 9.5, 9.0 Hz, 1H), 3.20 (dd, J = 11.0, 7.6 Hz, 1H), 3.37 (dd, J = 11.0, 3.8 Hz, 1H), 3.61 (dd, J = 15.3, 6.1 Hz, 1H), 3.81 (dddd, J = 15.3, 5.7, 1.6, 1.6 Hz, 1H), 3.80−3.97 (m, 4H), 4.26 (d, J = 4.3 Hz, 1H), 4.96 (dddd, J = 10.2, 1.4, 1.4, 1.4 Hz, 1H), 5.02 (dddd, J = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.54 (dddd, J = 17.2, 10.2, 5.8, 5.8 Hz, 1H); Selected NOEs are between δ 2.86 (H-3) and δ 3.20, 3.37 (CH_2Cl) and between δ 2.91 (H-4) and δ 4.26 ($CH(CO_2Et)_2$); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.9 (q × 2), 36.5 (d), 45.1 (d), 45.3 (t), 47.5 (t), 48.8 (t), 51.6 (d), 61.5 (t), 61.6 (t), 117.5 (t), 132.6 (d), 168.1 (s), 168.8 (s), 171.4 (s); Selected HMBC correlations are between δ 2.86 (H-3) and δ 51.6 ($CH(CO_2Et)_2$), 36.5 (C-4), 47.5 (CH_2Cl), between δ 2.79, 3.19 (H-5) and δ 36.5 (C-4), 47.5 (CH_2Cl), between δ 4.26 ($CH(CO_2Et)_2$) and δ 45.1 (C-3), 36.5 (C-4), and between δ 3.20, 3.37 (CH_2Cl) and δ 48.8 (C-5), 45.1 (C-3), 36.5 (C-4); IR (neat) 2983, 1733, 1694, 1645, 1491, 1450, 1373, 1274, 1176, 1176, 1031 cm^{-1}; MS (EI) m/z 333 (M^+, 26), 331 (M^+, 72), 282 (100), 190 (96%); HRMS M^+ 331.1188, 333.1154 (calcd for $C_{15}H_{22}ClNO_5$ 331.1187, 333.1157).

Diethyl 2-(*trans*-1-allyl-4-(bromomethyl)-2-oxopyrrolidin-3-yl)malonate (9e). (Table 2, entry 14, 0.5 mmol scale, 128 mg, 71%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.92−2.99 (m, 2H), 3.22 (dd, J = 9.8, 5.7 Hz, 1H), 3.46 (dd, J = 10.3, 7.0 Hz, 1H), 3.55 (dd, J = 9.8, 9.4 Hz, 1H), 3.61 (dd, J = 10.3, 3.7 Hz, 1H), 3.90 (dddd, J = 15.2, 6.0, 1.2, 1.2 Hz, 1H), 3.94 (dddd, J = 15.2, 6.0, 1.4, 1.4 Hz, 1H), 4.07 (d, J = 3.8 Hz, 1H), 4.14−4.30 (m, 4H), 5.22 (dddd, J = 10.1, 1.3, 1.3, 1.3 Hz, 1H), 5.25 (dddd, J = 17.2, 1.5, 1.5, 1.5 Hz, 1H), 5.73 (dddd, J = 17.2, 10.1, 6.0, 6.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.05 (q), 14.08 (q), 35.8 (d), 37.0 (t), 45.5 (t), 46.3 (d), 50.2 (t), 51.2 (d), 61.8 (t), 62.0 (t), 118.4 (t), 131.9 (d), 167.8 (s), 168.6 (s), 171.9 (s); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.862 (t, J = 7.1 Hz, 3H), 0.901 (t, J = 7.1 Hz, 3H), 2.74 (dd, J = 9.6, 6.0 Hz, 1H), 2.83 (dd, J = 7.7, 4.4 Hz, 1H), 2.93 (ddddd, J = 8.7, 7.7, 7.7, 6.0, 3.7 Hz, 1H), 3.04 (dd, J = 10.2, 7.7 Hz, 1H), 3.18 (dd, J = 9.6, 8.7 Hz, 1H), 3.24 (dd, J = 10.2, 3.7 Hz, 1H), 3.60 (dd, J = 15.4, 6.0 Hz, 1H), 3.80 (dddd, J = 15.4, 5.7, 1.6, 1.6 Hz, 1H), 3.80−3.96 (m, 4H), 4.27 (d, J = 4.4 Hz, 1H), 4.96 (dddd, J = 10.3, 1.4, 1.4, 1.4 Hz, 1H), 5.00 (dddd, J = 17.2, 1.6, 1.6, 1.6 Hz, 1H), 5.54 (dddd, J = 17.2, 10.3, 6.0, 5.7 Hz, 1H); Selected NOEs are between δ 2.83 (H-3) and δ 3.04, 3.24 (CH_2Br) and between δ 2.93 (H-4) and δ 4.27 ($CH(CO_2Et)_2$), 3.18 (H-5b); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 13.85 (q), 13.87 (q), 36.3 (d), 36.9 (t), 45.3 (t), 46.4 (d), 49.9 (t), 51.5 (d), 61.5 (t), 61.6 (t), 117.5 (t), 132.6 (d), 168.1 (s), 168.8 (s), 171.4 (s); Selected HMBC correlations are between δ 2.83 (H-3) and δ 51.5 ($CH(CO_2Et)_2$), 36.3 (C-4), 36.9 (CH_2Br), between δ 2.74, 3.18 (H-5a,b) and δ 36.3 (C-4), between δ 4.27 ($CH(CO_2Et)_2$) and δ 46.4 (C-3), 36.3 (C-4), and between δ 3.04, 3.24 (CH_2Br) and δ 49.9 (C-5), 46.4 (C-3); IR (neat) 2981, 1734, 1696, 1645, 1491, 1448, 1374, 1265, 1033 cm^{-1}; MS (EI) m/z 377 (M^+, 53), 375 (M^+, 53), 332 (41), 330 (38), 296 (56), 282 (100%); HRMS M^+ 375.0689, 377.0665 (calcd for $C_{15}H_{22}BrNO_5$ 375.0681, 377.0661). Anal. Calcd for $C_{15}H_{22}BrNO_5$: C, 47.88; H, 5.89; N, 3.72. Found: C, 48.14; H, 6.00; N, 3.74.

Diethyl 2-(*trans*-1-allyl-4-(iodomethyl)-2-oxopyrrolidin-3-yl)malonate (9f). (Table 2, entry 16, 0.5 mmol scale, 164 mg, 77%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.71 (ddddd, J = 8.8, 7.9, 7.5, 6.0, 3.7 Hz, 1H), 2.84 (dd, J = 7.5, 4.2 Hz, 1H), 3.08 (dd, J = 9.9, 6.0 Hz, 1H), 3.24 (dd, J = 10.1, 7.9 Hz, 1H), 3.42 (dd, J = 10.1, 3.7 Hz, 1H), 3.53 (dd, J = 9.9, 8.8 Hz, 1H), 3.89 (dd, J = 15.2, 6.0 Hz, 1H), 3.94 (dddd, J = 15.2, 4.5, 1.4, 1.4 Hz, 1H), 4.05 (d, J = 4.2 Hz, 1H), 4.14−4.31 (m, 4H), 5.22 (dddd, J = 10.1, 1.3, 1.3, 1.3 Hz, 1H), 5.25 (dddd, J = 17.2, 1.4, 1.4, 1.4 Hz, 1H), 5.73 (dddd, J = 17.2, 10.1, 6.0, 6.0 Hz, 1H); Selected NOEs are between δ 2.84 (H-3) and δ 3.24, 3.42 (CH_2I), between δ 2.71 (H-4) and δ 4.05 ($CH(CO_2Et)_2$), 3.53 (H-5b), and between δ 3.08 (H-5a) and δ 3.24, 3.42 (CH_2I); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.8 (t), 14.07 (q), 14.12 (q), 35.7 (d), 45.5 (t), 48.4 (d), 51.0 (d), 52.4 (t), 61.8 (t), 62.0 (t), 118.5 (t), 131.9 (d), 167.9 (s), 168.6 (s), 172.1 (s); Selected HMBC correlations are between δ 2.84 (H-3) and δ 51.0 ($CH(CO_2Et)_2$), 35.7 (C-4), 11.8 (CH_2I), between δ 3.08, 3.53 (H-5a,b) and δ 35.7 (C-4), between δ 4.05 ($CH(CO_2Et)_2$) and δ 35.7 (C-4), and between δ 3.24, 3.42 (CH_2I) and δ 52.4 (C-5); IR (neat) 2982, 1731, 1694, 1645, 1489, 1447, 1372, 1270, 1178, 1159, 1033 cm^{-1}; MS (EI) m/z 423 (M^+, 21), 378 (23), 296 (100%); HRMS M^+ 423.0548 (calcd for $C_{15}H_{22}INO_5$ 423.0543).

Diethyl 2-(*trans*-4-(chloromethyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (9g). (Table 2, entry 18, 0.5 mmol scale, 163 mg, 98%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.908 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 1.57 (qt, J = 7.4, 7.4 Hz, 2H), 2.91−2.98 (m, 2H), 3.21- 3.32 (m, 3H), 3.55−3.61 (m, 2H), 3.72 (dd, J = 11.0, 3.7 Hz, 1H), 4.07 (d, J = 4.0 Hz, 1H), 4.13−4.29 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ

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(ppm) 11.3 (q), 14.08 (q), 14.10 (q), 20.3 (t), 36.1 (d), 44.5 (t), 45.2 (d), 47.7 (t), 49.4 (t), 51.3 (d), 61.8 (t), 62.0 (t), 168.0 (s), 168.7 (s), 172.0 (s); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.744 (t, J = 7.3 Hz, 3H), 0.869 (t, J = 7.1 Hz, 3H), 0.904 (t, J = 7.1 Hz, 3H), 1.26 (qt, J = 7.3, 7.3 Hz, 2H), 2.76 (dd, J = 9.5, 5.9 Hz, 1H), 2.84 (dd, J = 7.3, 4.4 Hz, 1H), 2.92 (m, 1H), 3.02 (dt, J = 13.7, 6.9 Hz, 1H), 3.08−3.23 (m, 3H), 3.41 (dd, J = 11.1, 3.9 Hz, 1H), 3.80−3.97 (m, 4H), 4.27 (dd, J = 4.4, 1.8 Hz, 1H); Selected NOEs are between δ 2.84 (H-3) and δ 3.08−3.23 (overlapped), 3.41 (CH_2Cl) and between δ 2.92 (H-4) and δ 4.27 ($CH(CO_2Et)_2$); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 11.3 (q), 13.9 (q × 2), 20.5 (t), 36.6 (d), 44.3 (t), 45.3 (d), 47.7 (t), 49.1 (t), 51.6 (d), 61.4 (t), 61.6 (t), 168.1 (s), 168.8 (s), 171.5 (s); Selected HMBC correlations are between δ 2.84 (H-3) and δ 51.6 ($CH(CO_2Et)_2$), 36.6 (C-4), 47.7 (CH_2Cl), between δ 2.76 (H-5a) and δ 36.6 (C-4), 47.7 (CH_2Cl), between δ 4.27 ($CH(CO_2Et)_2$) and δ 45.3 (C-3), 36.6 (C-4), and between δ 3.41 (CHHCl) and δ 49.1 (C-5), 45.3 (C-3), 36.6 (C-4); IR (neat) 2970, 1734, 1694, 1493, 1456, 1373, 1274, 1373, 1274, 1178, 1033 cm^{-1}; MS (EI) m/z 335 (M$^+$, 32), 333 (M$^+$, 91), 305 (53), 284 (100%); HRMS M$^+$ 333.1344 (calcd for $C_{15}H_{24}ClNO_5$ 333.1343).

Diethyl 2-(*trans*-4-(bromomethyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (9h). (Table 2, entry 20, 0.5 mmol scale, 167 mg, 88%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.910 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.57 (qt, J = 7.3, 7.3 Hz, 2H), 2.89−2.98 (m, 2H), 3.21−3.32 (m, 3H), 3.45 (dd, J = 10.3, 7.1 Hz, 1H), 3.58 (dd, J = 9.5, 9.5 Hz, 1H), 3.61 (dd, J = 10.3, 3.5 Hz, 1H), 4.06 (d, J = 4.0 Hz, 1H), 4.13−4.30 (m, 4H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.3 (q), 14.07 (q), 14.10 (q), 20.4 (t), 35.9 (d), 37.1 (t), 44.5 (t), 46.5 (d), 50.6 (t), 51.2 (d), 61.8 (t), 61.9 (t), 167.9 (s), 168.7 (s), 172.0 (s); ^{1}H NMR (400 MHz, C_6D_6) δ (ppm) 0.745 (t, J = 7.3 Hz, 3H), 0.864 (t, J = 7.1 Hz, 3H), 0.900 (t, J = 7.1 Hz, 3H), 1.27 (qt, J = 7.3, 7.3 Hz, 2H), 2.71 (dd, J = 9.6, 6.0 Hz, 1H), 2.81 (dd, J = 7.5, 2.9 Hz, 1H), 2.94 (ddddd, J = 8.6, 7.9, 7.5, 6.0, 3.7 Hz, 1H), 2.98−3.12 (m, 2H), 3.04 (dd, J = 10.1, 7.9 Hz, 1H), 3.14 (dd, J = 9.6, 8.6 Hz, 1H), 3.29 (dd, J = 10.1, 3.7 Hz, 1H), 3.80−4.00 (m, 4H), 4.28 (d, J = 4.4 Hz, 1H); Selected NOEs are between δ 2.81 (H-3) and δ 3.04, 3.29 (CH_2Br) and between δ 2.94 (H-4) and δ 4.28 ($CH(CO_2Et)_2$), and between δ 2.71 (H-5a) and δ 3.29 (CHHBr); ^{13}C NMR (100.6 MHz, C_6D_6) δ (ppm) 11.3 (q), 13.86 (q), 13.87 (q), 20.5 (t), 36.4 (d), 37.1 (t), 44.3 (t), 46.6 (d), 50.3 (t), 51.5 (d), 61.5 (t), 61.6 (t), 168.1 (s), 168.8 (s), 171.5 (s); Selected HMBC correlations are between δ 2.81 (H-3) and δ 51.5 ($CH(CO_2Et)_2$), 36.4 (C-4), 37.1 (CH_2Br), between δ 2.71 (H-5a) and δ 37.1 (CH_2Br), between δ 4.28 ($CH(CO_2Et)_2$) and δ 46.6 (C-3), 36.4 (C-4), and between δ 3.04, 3.29 (CH_2Br) and δ 50.3 (C-5); IR (neat) 2966, 2935, 1732, 1694, 1490, 1453, 1372, 1267, 1176, 1035 cm^{-1}; MS (EI) m/z 380 ([M + 1]$^+$, 15), 378 ([M + 1]$^+$, 16), 85 (84), 83 (100%); HRMS M$^+$ 377.0838, 379.0823 (calcd for $C_{15}H_{24}BrNO_5$ 377.0838, 379.0817).

Diethyl 2-(*trans*-4-(iodomethyl)-1-propyl-2-oxopyrrolidin-3-yl)malonate (9i). (Table 2, entry 22, 0.5 mmol scale, 184 mg, 87%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.913 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.57 (qt, J = 7.4, 7.4 Hz, 2H), 2.70 (ddddd, J = 8.6, 8.1, 7.3, 5.9, 3.6 Hz, 1H), 2.82 (dd, J = 7.3, 4.2 Hz, 1H), 3.11 (dd, J = 9.9, 5.9 Hz, 1H), 3.23 (dd, J = 10.0, 8.1 Hz, 1H), 3.23−3.32 (m, 2H), 3.43 (dd, J = 10.0, 3.6 Hz, 1H), 3.56 (dd, J = 9.9, 8.6 Hz, 1H), 4.05 (d, J = 4.2 Hz, 1H), 4.13−4.30 (m, 4H); Selected NOEs are between δ 2.82 (H-3) and δ 3.23, 3.43 (CH_2I), between δ 2.70 (H-4) and δ 4.05 ($CH(CO_2Et)_2$), 3.56 (H-5b), and between δ 3.11 (H-5a) and δ 3.23, 3.43 (CH_2I); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 11.3 (q), 11.9 (t), 14.09 (q), 14.13 (q), 20.4 (t), 35.8 (d), 44.6 (t), 48.6 (d), 51.1 (d), 52.9 (t), 61.8 (t), 62.0 (t), 167.9 (s), 168.7 (s), 172.2 (s); Selected HMBC correlations are between δ 2.82 (H-3) and δ 51.1 ($CH(CO_2Et)_2$), 35.8 (C-4), 11.9 (CH_2I), between δ 3.11, 3.56 (H-5a,b) and δ 35.8 (C-4), 11.9 (CH_2I), between δ 4.05 ($CH(CO_2Et)_2$) and δ 48.6 (C-3), 35.8 (C-4), and between δ 3.23, 3.43 (CH_2I) and δ 52.9 (C-5); IR (neat) 2965, 2934, 1732, 1694, 1489, 1450, 1372, 1269, 1177, 1158, 1033 cm^{-1}; MS (EI) m/z 426 ([M + 1]$^+$); HRMS M$^+$ 425.0706 (calcd for $C_{15}H_{24}INO_5$ 425.0699).

Transformation of 2a to 10. A solution of compound **2a** (158 mg, 0.54 mmol), Bu_3SnH (313 mg, 290 μL, 1.08 mmol), and AIBN (17.4 mg, 0.108 mmol) in benzene (3.3 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 **10** (137 mg, 98%).

10: colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (d, J = 6.4 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.73−2.84 (m, 2H), 3.80 (dd, J = 8.9, 8.9 Hz, 1H), 3.90 (d, J = 4.6 Hz, 1H), 4.20−4.30 (m, 2H), 4.48 (dd, J = 8.9, 7.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 17.4 (q), 33.2 (d), 46.5 (d), 50.6 (d), 62.03 (t), 62.04 (t), 73.1 (t), 167.4 (s), 167.7 (s), 176.6 (s); Selected HMBC correlations are between δ 3.80, 4.48 (H-5) and δ 33.2 (C-4), between δ 4.48 ($CH(CO_2Et)_2$) and δ 46.5 (C-3), 33.2 (C-4), and between δ 1.14 (CH_3) and δ 73.1 (C-5), 46.5 (C-3), 33.2 (C-4); IR (neat) 2983, 1777, 1736, 1466, 1391, 1372, 1252, 1176, 1024 cm^{-1}; MS (CI) m/z 259 ([M + 1]$^+$); HRMS [M + 1]$^+$ 259.1183 (calcd for $C_{12}H_{19}O_6$ 259.1182) . Anal. Calcd for $C_{12}H_{18}O_6$: C, 55.81; H, 7.02. Found: C, 55.91; H, 7.15.

11: (0.2 mmol scale, 34 mg, 60%); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.13 (d, J = 6.8 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 2.54 (ddqd, J = 8.5, 7.9, 6.8, 6.5 Hz, 1H), 2.68 (ddq, J = 7.9, 5.0, 0.7 Hz, 1H), 2.85 (d, J = 0.7 Hz, 3H), 2.93 (dd, J = 9.4, 6.5 Hz, 1H), 3.50 (dd, J = 9.4, 8.5 Hz, 1H), 3.90 (d, J = 5.0 Hz, 1H), 4.13−4.29 (m, 4H); Selected NOEs are between δ 2.68 (H-3) and δ 1.13 (CH_3), between δ 2.54 (H-4) and δ 3.90 ($CH(CO_2Et)_2$), 3.50 (H-5b), and between 2.93 (H-5a) and 1.13 (CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.05 (q), 14.10 (q), 19.9 (q), 29.5 (d), 29.8 (q), 49.3 (d), 51.4 (d), 55.6 (t), 61.5 (t), 61.6 (t), 168.1 (s), 168.6 (s), 173.3 (s); Selected HMBC correlations are between δ 2.68 (H-3) and δ 51.4 ($CH(CO_2Et)_2$), 29.5 (C-4), 19.9 (CH_3), between δ 2.54 (H-4) and δ 55.6 (C-5), 51.4 ($CH(CO_2Et)_2$), 49.3 (C-3), 19.9 (CH_3), between δ 2.93, 3.50 (H-5a,b) and δ 29.5 (C-4), 19.9 (CH_3), between δ 3.90 ($CH(CO_2Et)_2$) and δ 49.3 (C-3), 29.5 (C-4), and between δ 1.13 (CH_3) and δ 55.6 (C-5), 49.3 (C-3), 29.5 (C-4); IR (neat) 2980, 1733, 1696, 1501, 1444, 1372, 1270, 1157, 1032 cm^{-1}; MS (EI) m/z 271 (M$^+$, 31), 226 (18), 152 (64), 124 (100%); HRMS M$^+$ 271.1416 (calcd for $C_{13}H_{21}NO_5$ 271.1420). Anal. Calcd for $C_{13}H_{21}NO_5$: C, 57.55; H, 7.80; N, 5.16. Found: C, 57.37; H, 7.83; N, 5.07.

Diethyl 2-(*t*-4-(chloromethyl)-*c*-5-methyl-2-oxotetrahydrofuran-*r*-3-yl)malonate (13). A 1.3:1 (**13**:**7a**) mixture (eq 7, 1 equiv of $AlCl_3$, 0.5 mmol scale, 80 mg, combined yield 52%); colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) peaks for **13**, 1.27−1.34 (m, 6H), 1.53 (d, J = 6.2 Hz, 3H), 2.81 (ddt, J = 10.1, 8.2, 4.2 Hz, 1H), 3.29 (dd, J = 10.1, 4.0 Hz, 1H), 3.69 (d, J = 4.2 Hz, 2H), 4.07 (d, J = 4.0 Hz, 1H); Selected NOEs are between δ 3.29 (H-3) and δ 3.69 (CH_2Cl), between δ 2.81 (H-4) and δ 4.07 ($CH(CO_2Et)_2$), 1.53 (CH_3), and between δ 4.52 (H-5) and δ 3.69 (CH_2Cl); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) peaks for **13**, 13.98 (q), 14.02 (q), 20.1 (q), 42.5 (d), 43.9 (t), 46.4 (d), 50.4 (d), 62.2 (t), 62.3 (t), 77.5 (d), 167.3 (s), 168.0 (s), 174.8 (s); Selected HMBC correlations are between δ 3.29 (H-3) and δ 50.4 ($CH(CO_2Et)_2$), 46.4 (C-4), between δ 4.52 (H-5) and δ 43.9 (CH_2Cl), between δ 3.69 (CH_2Cl) and δ 77.5 (C-5), and between δ 1.53 (CH_3) and δ 77.5 (C-5), 46.4 (C-4); IR (neat) 2984, 1779−1732, 1466, 1446, 1373, 1197, 1097, 1031 cm^{-1}; MS (CI) m/z 309 ([M + H]$^+$, 49%), 307 ([M + H]$^+$, 100%); HRMS M$^+$ 307.0941, 309.0924 (calcd for $C_{13}H_{20}ClO_6$ 307.0948, 309.0919).

Diethyl 2-(*trans*-4-(2-chloropropan-2-yl)-2-oxotetrahydrofuran-3-yl)malonate (15). (eq 8, $TiCl_4$, 0.5 mmol scale, 27 mg, isolated yield 17%); pale yellow oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.54 (s, 3H), 1.56 (s, 3H), 2.78 (ddd, J = 8.8, 5.7, 4.6 Hz, 1H), 3.18 (dd, J = 5.7, 4.1 Hz, 1H), 4.00 (d, J = 4.1 Hz, 1H), 4.15−4.33 (m, 4H), 4.47 (dd, J = 9.3, 4.6 Hz, 1H), 4.57 (dd, J = 9.3, 8.8 Hz, 1H); Selected NOEs are between δ 3.18 (H-3) and δ 1.54, 1.56 (C(CH_3)$_2$Cl) and between δ 2.78 (H-4) and δ 4.00 ($CH(CO_2Et)_2$), 4.57 (H-5b); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 29.9 (q), 30.2 (q), 42.1 (d), 49.4 (d), 52.9 (d), 62.3 (t), 62.4 (t), 69.1 (t), 70.6 (s), 167.4 (s), 167.8 (s), 176.2 (s); Selected HMBC correlations are between δ 3.18 (H-3) and

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δ 70.6 ($C(CH_3)_2Cl$), 52.9 ($CH(CO_2Et)_2$), 49.4 (C-4) and between δ 4.47, 4.57 (H-5a,5b) and δ 70.6 ($C(CH_3)_2Cl$), 176.2 (C-2); IR (neat) 2984, 1778, 1735, 1467, 1393, 1374, 1182, 1034 cm^{-1}; MS (EI) *m/z* 322 (M^+, 2.7), 320 (M^+, 7.5), 285 (100), 275 (41), 243 (74%); HRMS M^+ 320.1027, 322.1005 (calcd for $C_{14}H_{21}ClO_6$ 320.1027, 322.0997).

Diethyl 2-(*trans*-4-(propen-2-yl)-2-oxotetrahydrofuran-3-yl)-malonate (16). (eq 9, $AlCl_3$, 0.5 mmol scale, 27 mg, isolated yield 19%); pale yellow oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.276 (t, *J* = 7.1 Hz, 3H), 1.280 (t, *J* = 7.1 Hz, 3H), 1.75 (dd, *J* = 1.5, 0.7 Hz, 3H), 3.25 (dd, *J* = 10.8, 5.5 Hz, 1H), 3.50 (ddd, *J* = 10.8, 9.3, 8.9 Hz, 1H), 3.84 (d, *J* = 5.5 Hz, 1H), 4.00 (dd, *J* = 9.3, 9.3 Hz, 1H), 4.14–4.25 (m, 4H), 4.46 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.89 (qd, *J* = 0.7, 0.7 Hz, 1H), 4.91 (qd, *J* = 1.5, 1.5 Hz, 1H); Selected NOEs are between δ 3.25 (H-3) and δ 4.89 (=C*H*H), 1.75 ($C(CH_3)$=CH_2), between δ 3.50 (H-4) and δ 3.84 ($CH(CO_2Et)_2$), 4.46 (H-5b), and between δ 4.00 (H-5a) and δ 1.75 ($C(CH_3)$=CH_2); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 18.6 (q), 42.1 (d), 45.9 (d), 50.4 (d), 61.9 (t), 62.0 (t), 70.0 (t), 115.1 (t), 140.5 (s), 167.3 (s), 167.4 (s), 176.0 (s); Selected HMBC correlations are between δ 3.25 (H-3) and δ 50.4 ($CH(CO_2Et)_2$), 45.9 (C-4), between δ 3.50 (H-4) and δ 42.1 (C-3), and between δ 4.00, 4.46 (H-5a,5b) and δ 45.9 (C-4); IR (neat) 2982, 1779, 1734, 1647, 1372, 1263, 1163, 1032 cm^{-1}; MS (EI) *m/z* 285 ($[M + 1]^+$, 54), 239 (37), 85 (98), 83 (100%); HRMS M^+ 284.1259 (calcd for $C_{14}H_{20}O_6$ 284.1260).

Diethyl 2-(*t*-5-chloro-5-methyl-2-oxo-2*H*-tetrahydropyran-*r*-3-yl)malonate (19). (eq 10, 0.5 mmol scale, 108 mg, 70%); colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.67 (s, 3H), 2.20 (ddd, *J* = 13.9, 7.1, 3.1 Hz, 1H), 2.34 (dd, *J* = 13.9, 11.7 Hz, 1H), 3.45 (ddd, *J* = 11.7, 7.1, 4.6 Hz, 1H), 4.19 (d, *J* = 4.6 Hz, 1H), 4.17–4.29 (m, 4H), 4.33 (dd, *J* = 12.1 Hz, 1H); Selected NOEs are between δ 3.45 (H-3) and δ 2.20 (H-4a), between δ 2.34 (H-4b) and δ 4.43 (H-6b), 1.67 (CH_3), and between δ 4.43 (H-6b) and δ 1.67 (CH_3); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 28.3 (q), 37.6 (d), 38.5 (t), 52.3 (d), 62.08 (t), 62.13 (t), 63.9 (s), 77.5 (t), 167.8 (s), 168.2 (s), 169.6 (s); Selected HMBC correlations are between δ 3.45 (H-3) and δ 169.6 (C-2), 38.5 (C-4), between δ 2.20, 2.34 (H-4a,4b) and δ 169.6 (C-2), 37.6 (C-3), and between δ 4.33, 4.43 (H-6a,6b) and δ 169.6 (C-2), 63.9 (C-5); IR (neat) 2983, 1738, 1464, 1448, 1373, 1332, 1274, 1213, 1179, 1032 cm^{-1}; MS (EI) *m/z* 308 (M^+, 0.6%), 306 (M^+, 1.4), 271 (100%); HRMS M^+ 306.0871, 308.0851 (calcd for $C_{13}H_{19}ClO_6$ 306.0870, 308.0841).

20: Compound **20** is unstable to column chromatography (SiO_2) and contains a small amount of starting material **18** (eq 11, 0.5 mmol scale, 64 mg, isolated yield 42%); colorless oil; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, *J* = 7.1 Hz, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.78 (narrow multiplet, 3H), 4.10 (d, *J* = 10.4 Hz, 1H), 4.17–4.31 (m, 4H), 4.61 (d, *J* = 13.0 Hz, 1H), 4.64 (d, *J* = 13.0 Hz, 1H), 4.84 (d, *J* = 10.4 Hz, 1H), 4.98 (m, 1H), 5.05 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.0 (q), 14.1 (q), 19.4 (q), 52.7 (d), 56.3 (d), 62.4 (t), 62.5 (t), 69.6 (t), 114.1 (t), 139.0 (s), 165.6 (s), 166.0 (s), 167.5 (s); IR (neat) 2984, 1748, 1659, 1447, 1370, 1306, 1258, 1164, 1028 cm^{-1}; MS (EI) *m/z* 309 ($[M + 1]^+$, 25), 307 ($[M + 1]^+$, 100%); HRMS M^+ 306.0872, 308.0846 (calcd for $C_{13}H_{19}ClO_6$ M^+ 306.0870, 308.0841).

■ ASSOCIATED CONTENT

Supporting Information

The additional proposed reaction mechanism for the model compounds, Cartesian coordinates of the optimized geometries, ^1H and ^{13}C NMR spectral data, and 2D NOESY spectra. This information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(11) Formation of **3** presumably arises from participation of adventitious water in situ.

(12) Use of 1 or 2 equiv of $SnCl_4$ or $ZnBr_2$ gave the starting material, and BCl_3 gave a complex mixture at room temperature.

(13) Snider and Roush assigned the stereochemistry using coupling constants $J_{3,4}$ by comparison with the reported data (9−12 Hz for 3,4-*trans*; 5.0−9.0 Hz for 3,4-*cis*). Savastianoff, D.; Pfau, M. *Bull. Soc. Chem. Fr.* **1967**, 4162. 3,4-*trans* coupling constants $J_{3,4}$ determined by NOESY for 2-oxotetrahydrofurans in this work range from 5.7 to 10.8 Hz (**2a** (8.4 Hz), **2b** (8.6 Hz), **7a** (8.0 Hz), **7b** (8.1 Hz, 8 Hz in ref 5), **13** (10.1 Hz), **15** (5.7 Hz), and **16** (10.8 Hz)).

(14) Chemical shifts of H-3 and H-4 for Cl- and Br-adducts **9a,b,d,e,g,h** are overlapped in $CDCl_3$. They are separated in C_6D_6.

(15) The 3,4-*trans* coupling constants $J_{3,4}$ (7.3−7.9 Hz) determined by NOESY for 2-oxopyrrolidines in this work (**9a** (7.5 Hz), **9b** (7.3 Hz), **9c** (7.2 Hz), **9d** (7.7 Hz), **9f** (7.5 Hz), **9g** (7.3 Hz), **9h** (7.5 Hz), **9i** (7.3 Hz), and **11** (7.9 Hz)) are in agreement with the reported data (J_{trans} = 6−8 Hz) for some 2-oxopyrrolidines. (a) Yang, D.; Lian, G.-Y.; Yang, H.-F.; Yu, J.-D.; Zhang, D.-W.; Gao, X. *J. Org. Chem.* **2009**, *74*, 8610. (b) Yang, D.; Yan, Y.-L.; Law, K.-L.; Zhu, N.-Y. *Tetrahedron* **2003**, *59*, 10465.

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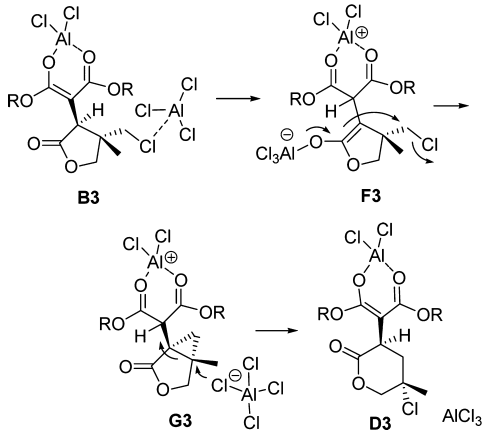

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