Lewis Acid Promoted Cyclization of Enyne Triesters and Diesters

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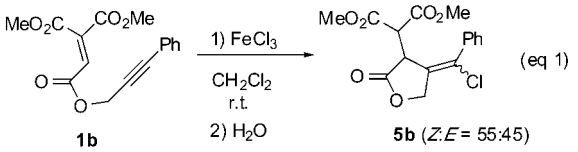
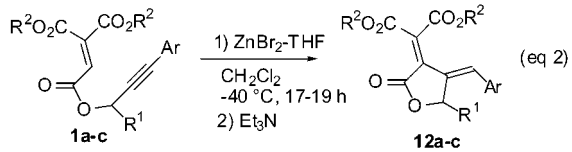
Reactions of enynes with three or two ester groups (**1**−**4**) in the presence of halogen-ligand Lewis acids gave cyclized products with halide incorporation (**5**−**8**) with high generality. The cyclization process was also analyzed in a theoretical study. Facile isomerization and dehydrohalogenation of five-membered products **5** and **8** by Al_2O_3 or Et_3N were also observed; this process introduces conjugated moieties into the products.

I. Introduction

Lewis acid promoted reactions have been extensively utilized for ring-forming reactions such as Diels−Alder reactions,[1] [2 + 2] cycloadditions,[2] ene reactions,[3] and alkene−alkene cyclizations.[4] Lewis acids play a major role in carbon−carbon bond-forming processes by coordinating to carbonyl compounds.[5] Recently, transition-metal-catalyzed cyclization reactions of enynes have been extensively studied for the construction of ring systems.[6] On the other hand, only a few examples of Lewis acid promoted cyclizations of enynes have been reported so far. Snider and Roush reported an example of cyclization of propargylic esters of ethenetricarboxylic acid **1** in the presence of $FeCl_3$ as an extension of ene−ene cyclization to give chlorinated γ-lactones (eq 1).[4a] Recently, we have





reported $ZnBr_2$(THF)-promoted cycloisomerizations of enynes **1** to give exocyclic conjugated dienes **12** (eq 2).[7]

Since the product types are different from those reported by Snider, we decided to explore Lewis acid promoted reactions of triester−enyne compounds systematically. The Lewis acid promoted enyne cyclization requires both that a highly electrophilic alkene has coordination sites for a Lewis acid and that the alkyne component can function as a nucleophile. Alkenes substituted with three or two carbonyl groups were designed as very electrophilic counterparts. To this end, application of this reaction toward the construction of oxygen- and nitrogen-containing heterocycles and carbocycles has been investigated.

We thus examined Lewis acid (MX_n) promoted intramolecular cyclizations of the designed diester- and triester-substituted alkenes **1**−**4**. Herein, we report a novel and general Lewis acid promoted intramolecular C−C bond-forming reaction to give halogenated five-membered cyclic compounds (eq 3). The elementary

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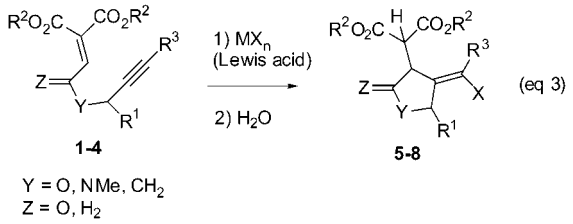
Table 1. Triester−Enyne Cyclization (in Eq 4)[a]

entry	substrate	R^1	R^2	Lewis acid	time (h)	X	**5** (yield (%))
1	**1a**	H	Et	$ZnBr_2$−THF	16	Br	**5a-Br** (52)
2	**1a**	H	Et	$FeCl_3$	3	Cl	**5a-Cl** (98)
3	**1b**	H	Me	$FeCl_3$	3	Cl	**5b-Cl** (83)
4	**1c**	Me	Et	$FeCl_3$	3	Cl	**5c-Cl** (63[b])

[a] Reactions were carried out using 0.4−0.8 mmol of **1a**−**c**, 1.2 equiv of $ZnBr_2$, and 1.0 equiv of THF or 1.2 equiv of $FeCl_3$ at 0.5 M for **1a**−**c** in CH_2Cl_2. [b] Diastereomer ratio: 7:3.

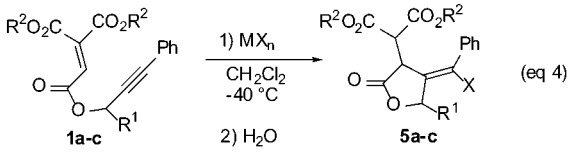
processes were also examined computationally to explore the structural and electronic factors required for ring closure.



(eq 3)

II. Results and Discussion of Cyclization Reaction

A. Cyclization of Triester−Enynes. As described in the Introduction, $ZnBr_2$(THF)-promoted cycloisomerization of enynes **1** gave cyclic dienes **12** (eq 2), which are different from the products of the $FeCl_3$-promoted reaction reported (eq 1).[4a] The decisive difference in the reaction conditions employed was the workup with Et_3N instead of H_2O. A workup procedure to remove Lewis acid by addition of an amine is usually used for Lewis acid promoted reactions in order to avoid highly acidic conditions in the presence of H_2O. However, the amine (Et_3N) may induce further transformation in this case. We have examined the reaction of **1a**−**c** with $ZnBr_2$ (1.2 equiv)−THF (1.0 equiv) or $FeCl_3$ (1.2 equiv) at −40 °C in CH_2Cl_2 and subsequent workup with H_2O (eq 4 and Table 1). The



(eq 4)

isolated products were the cyclized HBr and HCl adducts **5a**−**c** in 52−98% yield. Thus, workup with water is appropriate to obtain halogenated cyclic compounds. The reaction at −40 °C gave the (*Z*)-olefin products stereoselectively.[8] The *γ*-lactone structure of **5a**−**c** was suggested by the presence of a characteristic C=O absorption (1783−1792 cm^{-1}) and disappearance of the 2238−2244 cm^{-1} absorption for the C≡C triple bond in **1a**−**c**. ^1H, ^{13}C, $^1H/^{13}C$-HSQC, HMBC, and NOESY spectra were in agreement with the lactone structure shown in eq 4. The stereochemistry was determined by the NOEs observed between Ph and C*H*CH$(CO_2R^2)_2$. Compounds **5a**−**c** are unstable to silica gel column chromatography and are partially transformed to cyclic dienes **12a**−**c**. Compounds **5a**−**c** could be purified without dehydrohalogenation by preparative reverse-phase column chromatography (Cosmosil 75C18OPN, CH_3CN-H_2O).

(8) Snider obtained a 55:45 *Z* and *E* olefin mixture by the reaction of **1b** at room temperature.[4a]

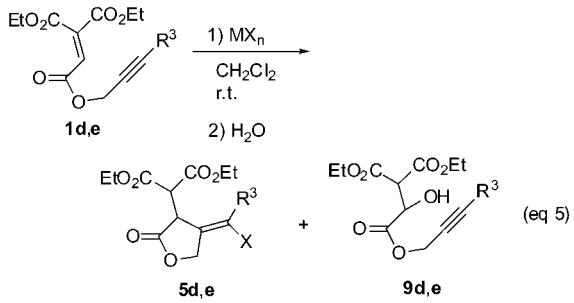
Table 2. Triester−Enyne Cyclization (in Eq 5)[a]

entry	substrate	R^3	Lewis acid	time (h)	X	**5** (yield (%))	**9** (yield (%))
1	**1d**	Me	$ZnBr_2$	16	Br	**5d-Br** (39)	**9d** (16)
2	**1d**	Me	$ZnBr_2$−THF	16	Br	**5d-Br** (37)	**9d** (30)
3	**1d**	Me	$FeCl_3$	3	Cl	**5d-Cl** (76)	
4	**1e**	Et	$ZnBr_2$	16	Br	**5e-Br** (37)	**9e** (29)
5	**1e**	Et	$FeCl_3$	3	Cl	**5e-Cl** (67)	
6	**1e**	Et	ZnI_2	16	I	**5e-I** (31)	**9e** (31)

[a] Reactions were carried out using 0.4−1.0 mmol of **1d**,**e**, 1.2 equiv of $ZnBr_2$, and 1.0 equiv of THF or 1.2 equiv of Lewis acid at 0.5 M for **1d**,**e** in CH_2Cl_2.

The diasteroselectivity of the products is not very high in the case of entry 4 in Table 1.

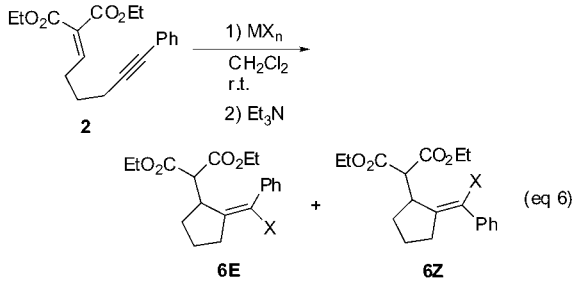
Reaction of **1d** and **1e** (R^3 = alkyl, see eq 5) in the presence of $ZnBr_2$ at room temperature for 16 h and subsequent treatment with water gave cyclized products **5d-Br** and **5e-Br** along with noncyclized H_2O adducts



(eq 5)

9d and **9e**, in 37−39% and 16−29% yields, respectively (entries 1 and 4, Table 2). Reaction in the presence of $FeCl_3$ at room temperature for 3 h gave the cyclized products **5d-Cl** and **5e-Cl** in 67−76% yields (entries 3 and 5). The olefin stereochemistry in cyclized products **5d**,**e** was detemined as *Z* by NOEs between R^3 and C*H*CH$(CO_2Et)_2$.

B. Diester−Enynes. Next, an alkene with only two ester groups, the enyne **2**, was examined (eq 6). Com-



(eq 6)

pound **2** was prepared by Knoevenagel condensation of diethyl malonate with 6-phenyl-5-hexynal. Reaction with $ZnBr_2$ or $FeCl_3$ in CH_2Cl_2 proceeded only when the reaction temperature was raised to room temperature. Workup with Et_3N gave the cyclopentane products **6E-Br** and **6E-Cl** in 64 and 56% yields, respectively (Table 3, entries 1 and 2). Other Lewis acids were also examined, and the results are shown in Table 3. In entries 3 and 5, the formation of (*Z*)-olefin product **6Z-Cl** was observed in low yields (note that the *E* and *Z* nomenclatures are opposite to those of the substrates **5** in terms of the X-addition orientation).

C. Diester/Amide−Enynes. Alkenes with two ester groups and an amide group (enynes **3a**,**b**) were designed

Table 3. Diester−Enyne Cyclization (in Eq 6)[a]

entry	Lewis acid	time (h)	X	**6** (yield (%))	**6E**:**6Z**
1	$ZnBr_2$	13	Br	**6E-Br** (64)	100:0
2	$FeCl_3$	15	Cl	**6E-Cl** (ca. 56)[b]	100:0
3	$AlCl_3$	16	Cl	**6E**,**Z-Cl** (31)	80:20
4	$ZrCl_4$	14	Cl	**6E-Cl** (46)	100:0
5	$GaCl_3$	15	Cl	**6E**,**Z-Cl** (23)	20:80
6	$ZnCl_2$	17	Cl	**6E** (26)	100:0

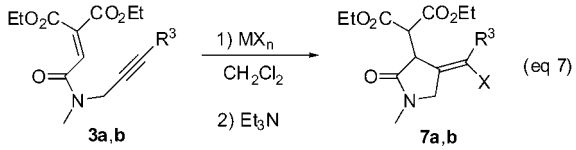
[a] Reactions were carried out using 0.1−0.4 mmol of **2** and 1.2 equiv of Lewis acid at 0.5 M for **2** in CH_2Cl_2. [b] A small amount of unidentified impurity could not be separated.

Table 4. Diester/Amide−Enyne Cyclization (in Eq 7)[a]

entry	sub-strate	R^3	Lewis acid	temp (°C)	time (h)	X	**7** (yield (%))
1	**3a**	Ph	$ZnBr_2$-THF	−40	16	Br	**7a-Br** (84)
2	**3a**	Ph	$ZnBr_2$	−40	19	Br	**7a-Br** (48)
3	**3a**	Ph	$FeCl_3$	−40	3	Cl	**7a-Cl** (42)
4	**3a**	Ph	$ZnCl_2$	−40	18	Cl	**7a-Cl** (64)
5	**3a**	Ph	ZnI_2	−40	17	I	**7a-I** (62)
6	**3b**	nPr	$ZnBr_2$	room temp	16	Br	**7b-Br** (74)
7	**3b**	nPr	$FeCl_3$	room temp	3	Cl	**7b-Cl** (69)
8	**3b**	nPr	$ZnCl_2$	room temp	16	Cl	**7b-Cl** (60)
9	**3b**	nPr	ZnI_2	room temp	17	I	**7b-I** (49)

[a] Reactions were carried out using 0.2−0.9 mmol of **3a**,**b**, 1.2 equiv of $ZnBr_2$, and 1.0 equiv of THF or 1.2 equiv of Lewis acid at 0.5 M for **3a**,**b** in CH_2Cl_2.

for the construction of nitrogen-containing heterocycles (eq 7). Compounds **3** were prepared by condensation of



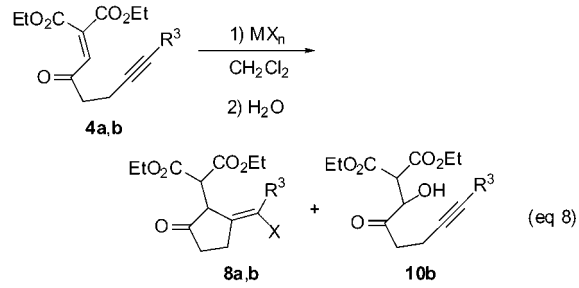
1,1-diethyl 2-hydrogen ethenetricarboxylate with the corresponding propargylamines. Reaction of the phenyl-substituted alkyne **3a** with $ZnBr_2$−THF in CH_2Cl_2 proceeded at −40 °C. Workup with Et_3N gave the brominated γ-lactam **7a-Br** in 84% yield (Table 4, entry 1). The yield of **7a** decreased when THF was omitted from the reaction (entry 2). Although the effect of THF is not clear, it is presumed that coordination of THF to Zn adjusts the strength of the Lewis acid and prevents side reactions.[9] Otherwise, THF can work as a scavenger of protons produced from trace amounts of water. Zinc chloride and zinc iodide promoted reactions also gave the corresponding halogenated γ-lactams in good yields (64% and 62% yields in entries 4 and 5, respectively). Reaction of *n*-propyl-substituted alkyne **3b** with $FeCl_3$ or zinc halides in CH_2Cl_2 proceeded at room temperature (entries 6−9).

D. Diester/Ketone−Enynes. Alkenes with two ester groups and one ketone group (enynes **4**) were next examined (eq 8, Table 5). The reaction is another example leading to carbocycles. Starting materials **4** were prepared by Wittig reaction of the corresponding carbonylmethylenetriphenylphosphorane with diethyl ketomalonate. Reaction of enynes **4** with $FeCl_3$ in CH_2Cl_2 proceeded at −40 °C. Workup with H_2O gave the chlorinated cyclopentanones **8a-Cl** and **8b-Cl** stereoselectively in 59−68% yields. Reaction of **4b** with $ZnBr_2$ required room temperature and gave the brominated cyclopentanone **8b-Br** in 47% yield along with the noncyclized H_2O adduct **10b** in 13% yield. Compounds **8a-Cl** and **8b-Cl** were also unstable to silica gel colum chromatography and partially transform to isomeric compounds (vide infra). The compounds **8a-Cl** and **8b-Cl** could be purified by preparative reverse-phase column chromatography (Cosmosil 75C18PREP for **8a-Cl** or Cosmosil 75C18OPN for **8b-Cl**, CH_3CN-H_2O).

Table 5. Diester/Ketone−Enyne Cyclization (in Eq 8)[a]

entry	sub-strate	R^3	Lewis acid	temp (°C)	time (h)	X	**8** (yield (%))	**10** (yield (%))
1	**4a**	Ph	$FeCl_3$	−40	3	Cl	**8a-Cl** (68)	
2	**4b**	Me	$FeCl_3$	−40	3	Cl	**8b-Cl** (59)	
3	**4b**	Me	$ZnBr_2$	room temp	16	Br	**8b-Br** (47)	**10b** (13)

[a] Reactions were carried out using 0.3 mmol of **4a**,**b** and 1.2 equiv of Lewis acid at 0.5 M for **4a**,**b** in CH_2Cl_2.



III. Reaction Mechanism for Formation of γ-Lactones

To clarify the precise features of the critical ring-forming step, a computational study for the reaction of the model compound **M1** with $ZnBr_2$ was carried out.[10] **M1** is different from **1d** only in the ester substituent R^2 (R^2 = Me for **M1** and R^2 = Et for **1d**). Geometries were fully optimized by the B3LYP density functional method[11] together with the SCRF[12] solvent effect (CH_2Cl_2, dielectric constant 8.93) using GAUSSIAN 98.[13] The basis set employed was 6-31G*.[14] Vibrational frequency calculations gave sole imaginary frequencies for transition structures, which verifies that the obtained geometries are correctly of the saddle point. All the intermediate species were calculated to have no imaginary frequencies. The computed energies are ΔH_0 (=ΔE + ZPVE).

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(10) The structures of Lewis acid-free **M1** conformers are shown in Figure 8S (Supporting Information).

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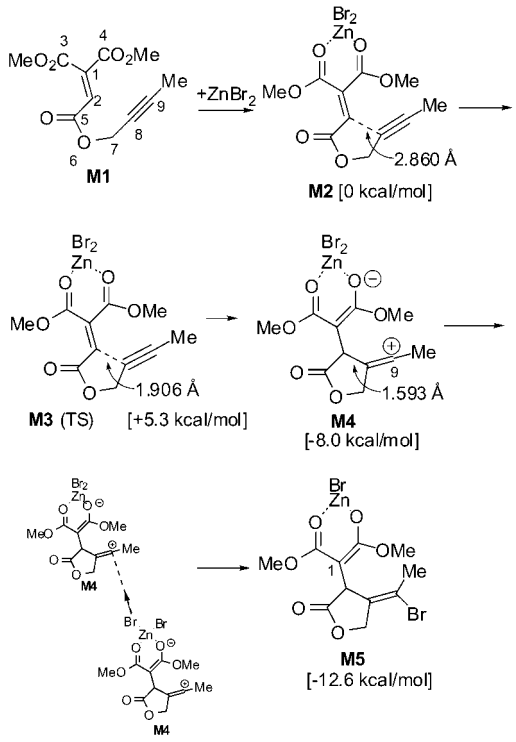
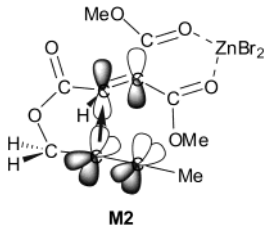
(14) All electrons of the metals were included.

Scheme 1. Mechanism of the Cyclization Calculated at B3LYP/6-31G* SCRF



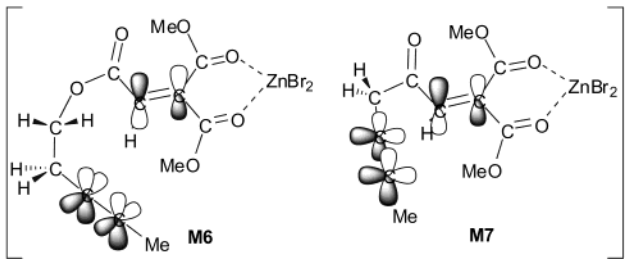
The mechanism was examined for γ-lactone ring formation and is shown in Scheme 1. Nucleophilic attack of the alkyne moiety (C_8) at the vinyl carbon (C_2) of the electrophilic olefin complexed with $ZnBr_2$ in **M2** gives the zwitterionic intermediate **M4** via the cyclization transition state (TS) **M3**.[15] Sequential intermolecular trans addition of halide ion (X^-) of the $ZnBr_2$ complex **M4** to a vinyl cation moiety of another **M4** may lead to intermediate **M5**. In **M4**, the cis Br^- addition to C_9 is sterically unfavorable, which leads to the trans-addition stereoselectivity in most cases.[16] Protonation of C_1 and removal of ZnBrOH from the intermediate **M5** yields the **5d** analogue of the bromo-γ-lactone product.

In the $ZnBr_2$ complex **M2**, the ring-forming C_2- - -C_8 distance is only 2.860 Å, and the structure has a

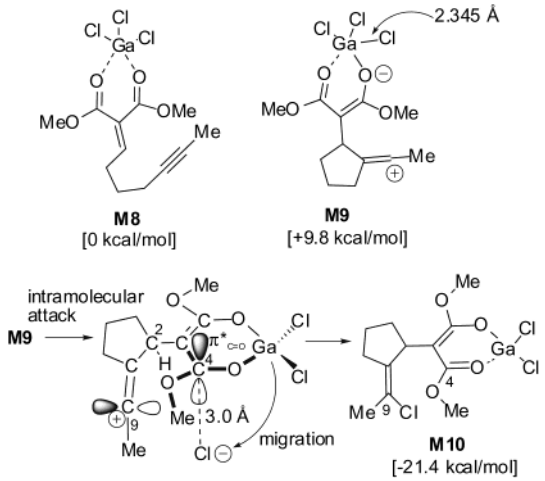


conformation which is oriented properly to cyclize (Figure 1, geometry at the top).[17] The ring formation transition state **M3** is shown in Figure 2. Geometry optimization using the 6-311G* basis set was also carried out for **M3**. The geometric parameters for **M3** calculated using B3LYP/6-311G* SCRF were similar to those calculated using B3LYP/6-31G* SCRF. The energy barrier for cyclization is +5.3 kcal/mol and indicates that the cyclization is a facile process. The structure of the resulting zwitterionic intermediate **M4** (Figure 5S in the Supporting Information) shows vinyl cation characteristics at C_9 (atomic charge +0.39). The alkyne group may be the key for facile five-membered-ring formation. The two perpendicular $2p_\pi$ orbitals of the triple bond as a nucleophile have spatial flexibility, and one of them can be directed flexibly and appropriately toward the electrophilic center in **M2** for the intramolecular charge transfer.

The corresponding precursors thought to give a six-membered ring (**M6**) and a four-membered ring (**M7**)



(16) As is the case of reaction of **2** with $GaCl_3$ and $AlCl_3$ in entries 3 and 6 of Table 3, Cl^- attack may occur intramolecularly (cis addition). The Lewis acids consisting of the group 13 elements such as $GaCl_3$ and $AlCl_3$ have a tendency to form stable four-coordinated carbonyl complexes.[5a] The five-coordinated anion intermediate **B** (see Scheme 3) is unstable for $GaCl_3$ and $AlCl_3$. In fact, the model calculation shows the anion intermediate model **M9** to be 9.8 kcal/mol less stable than the neutral precursor model **M8**. The stability rank is opposite to that of **M2** and **M4** (Scheme 1). The structures of **M8** and **M9** are shown in Figure 7S (Supporting Information). As seen in structure **M9**, one Ga−Cl bond length is longer than the others (2.345 Å vs 2.248 and 2.238 Å). Therefore, one Cl^- anion can be released readily to compensate the instability of **M9**, leading to the intramolecular Cl^- cis addition. We have made calculations to simulate the Cl^- migration route. After the tetravalent coordination of Ga pushes out a chloride ion in **M9**, it would be bound to a $\pi^*_{C=O}$ electrophilic carbon, C_4. The smaller ion radius of Cl^- compared to that of Br^- makes the internal migration of Cl^- possible. To examine the intermediacy of the $Cl^- \rightarrow \pi^*$ CT complex, we have made geometry optimizations with an assumed C_4- - -Cl^- distance of 3.0 Å. The initial geometry has been calculated to be converted to that of a neutral intermediate, **M10**, with a C_9−Cl covalent bond. Thus, the vacant orbital lobe of the vinyl cation, C_9, is electrophilic enough to attract Cl^- located at the intermediate region. In contrast to $GaCl_3$ and $AlCl_3$, the other Lewis acids examined form stable two carbonyl coordinated chelate intermediates such as **M4**, leading to exclusive intermolecular trans addition (Scheme 1).



(17) The linear conformer **M2I** (Figure 4S, in the Supporting Information) was also calculated and is 10.3 kcal/mol more stable than **M2**, probably due to steric reasons. However, the energy difference is small enough to proceed to cyclization, leading to the product **M5** (−12.6 kcal/mol). In addition, **M2I** is only 1.2 kcal/mol more stable than **M2** in the gas phase (without SCRF and ZPVE). **M2I** may be overstabilized by the SCRF solvent effect.

(15) The formation of hydrated byproducts **9** and **10b** is presumed to result from attack by trace amounts of water on the complex **M2** (corresponding to **A** in Scheme 3). Compounds **9** and **10b** were only observed with $ZnBr_2$ and ZnI_2 and not with $FeCl_3$. This is because the stronger Lewis acid, FeCl, facilitates the cyclization process but the weaker Lewis acids $ZnBr_2$ and ZnI_2 allow the alternative reaction: i.e., water addition to the double bond.

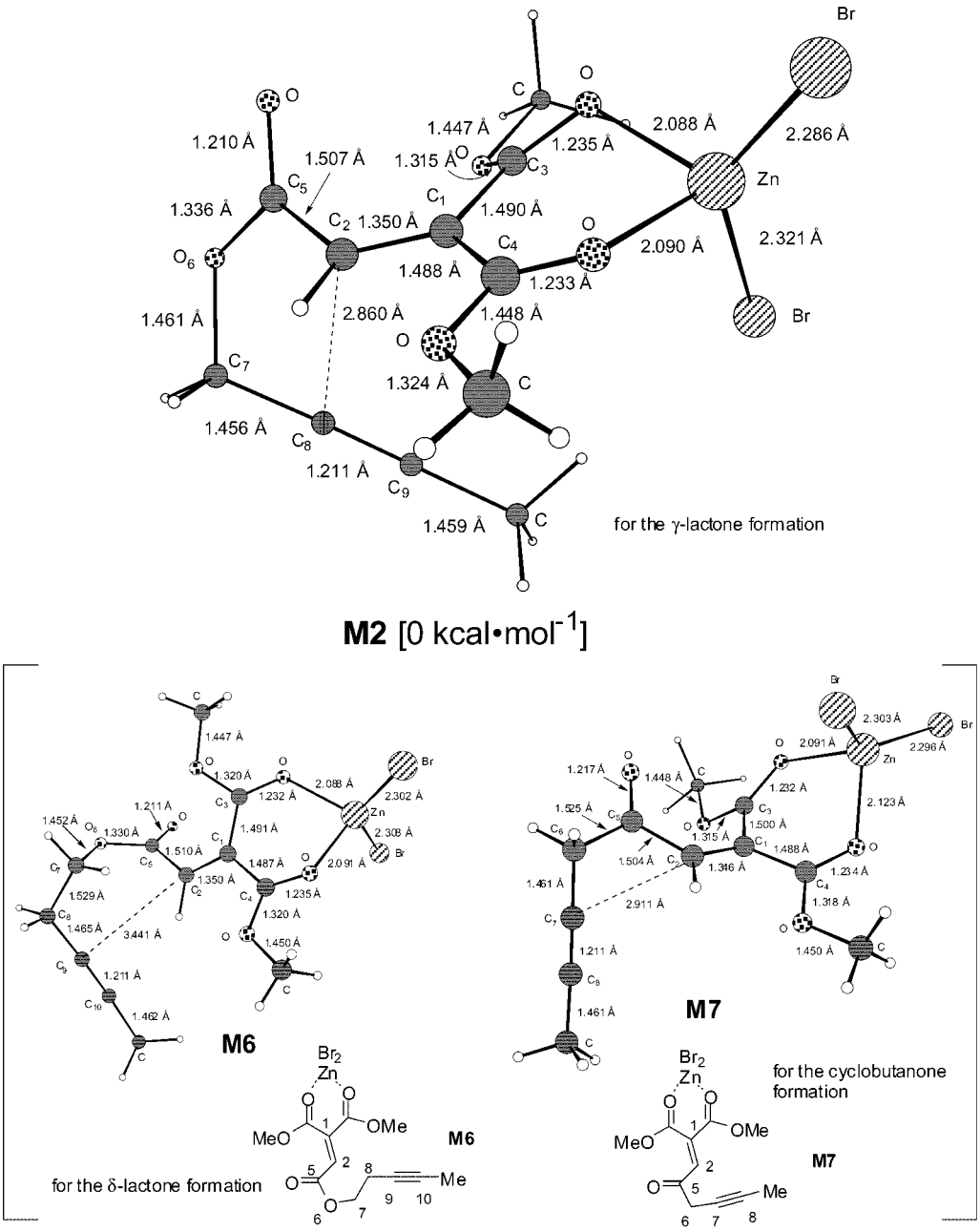
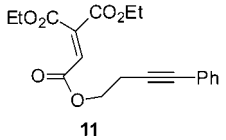


Figure 1. B3LYP/6-31G* SCRF-optimized geometries of precursor **M2** in Scheme 1 and for comparison two model precursors, **M6** and **M7**, to give a six-membered ring and a four-membered ring, respectively. Small white circles denote hydrogen atoms.

were also calculated (lower half of Figure 1). The ring-forming C_2- - -C_9 and C_2- - -C_7 distances are 3.441 and 2.911 Å, respectively. The $2p_\pi$ orbitals in **M6** and **M7** in the alkyne part are not directed properly toward the vinyl π^* orbital for σ-bond formation. The six- and four-membered-ring formations seem to be less efficient. Experimentally, cyclization of substrate **11** (vide infra)



11

was also examined. Reaction with $ZnBr_2$ at −40 °C or room temperature and with $FeCl_3$ at −40 °C gave only recovered starting material. Reaction with $FeCl_3$ at room temperature gave a complex mixture. Six-membered-ring formation was not an efficient process, as suggested by the calculation of **M6**. For four-membered-ring formation, strain in the product may interfere with the cyclization; however, this will be experimentally examined in the future.

Intermolecular trans addition of Br^- to the vinyl cation moiety of the zwitterionic intermediate **M4** was examined by calculation of the reaction between **M4** and a model, $Br_2Zn(CO_2Me)_2CCH_3^-$. This is because the size of a system composed of two **M4** intermediates is too large to be calculated by B3LYP/6-31G*, owing to restricted computer power. When the vinyl cation carbon (C_9) of **M4** and Br in $Br_2Zn(CO_2Me)_2CCH_3^-$ is set to 3.5 Å as an

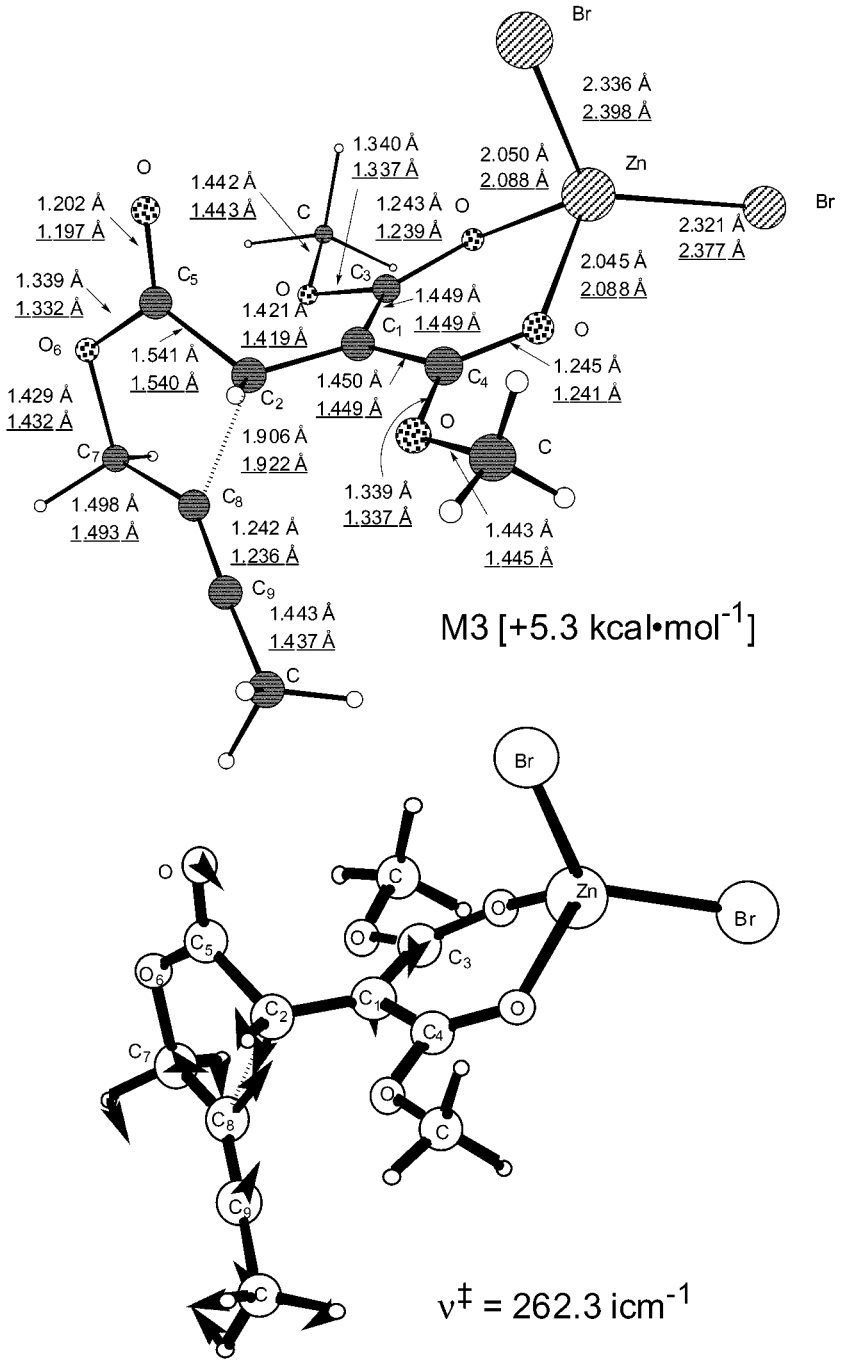


Figure 2. B3LYP/6-31G* SCRF-optimized geometry of transition state **M3** and reaction-coordinate vectors corresponding to the sole imaginary frequency $\nu^{\ddagger}$. The energy in brackets is relative to **M2**. Underlined numbers are obtained by B3LYP/6-311G* SCRF.

initial structure, the vinyl cation carbon (C_9) is linked readily with the bromide ion, as shown in the optimization process (Figure 3). Thus, the intermolecular Br^- relay may occur successively, leading to the complex **M5**, whose optimized structure is shown in Figure 6S (Supporting Information).

IV. Isomerization and Dehydrohalogenation of Cycloadducts

We observed that the $ZnBr_2$(THF)-promoted reaction of enynes **1a**−**c** and subsequent workup with Et_3N instead of H_2O gave the dialkylidene-γ-lactones **12a**−**c**

Table 6. Isomerization and Dehydrochlorination of Cyclized Products

compd	Y	R^3	conditions	product (yield (%))	$R^{3'}$
5a-Cl	O	Ph	Al_2O_3	**12a** (80)	
5a-Cl	O	Ph	Et_3N	**12a** (82)	
5d-Cl	O	Me	Al_2O_3	**12d** (54)	
5e-Cl	O	Et	Al_2O_3	**12e** (77)	
5d-Cl	O	Me	Et_3N	**17d** (quant)	H
5e-Cl	O	Et	Et_3N	**17e** (80)	Me
8b-Cl	CH_2	Me	SiO_2 (15% H_2O)	**13b-Cl** (99)	
8b-Cl	CH_2	Me	Al_2O_3	**14b** (57)	
8b-Cl	CH_2	Me	Et_3N	**15b** (26)	H
13b-Cl	CH_2	Me	Al_2O_3(15% H_2O)	**15b** (quant)	H
14b	CH_2	Me	Et_3N, 3 h	**15b** (quant)	H
8a-Cl	CH_2	Ph	in $CDCl_3$	**13a-Cl** (quant)	

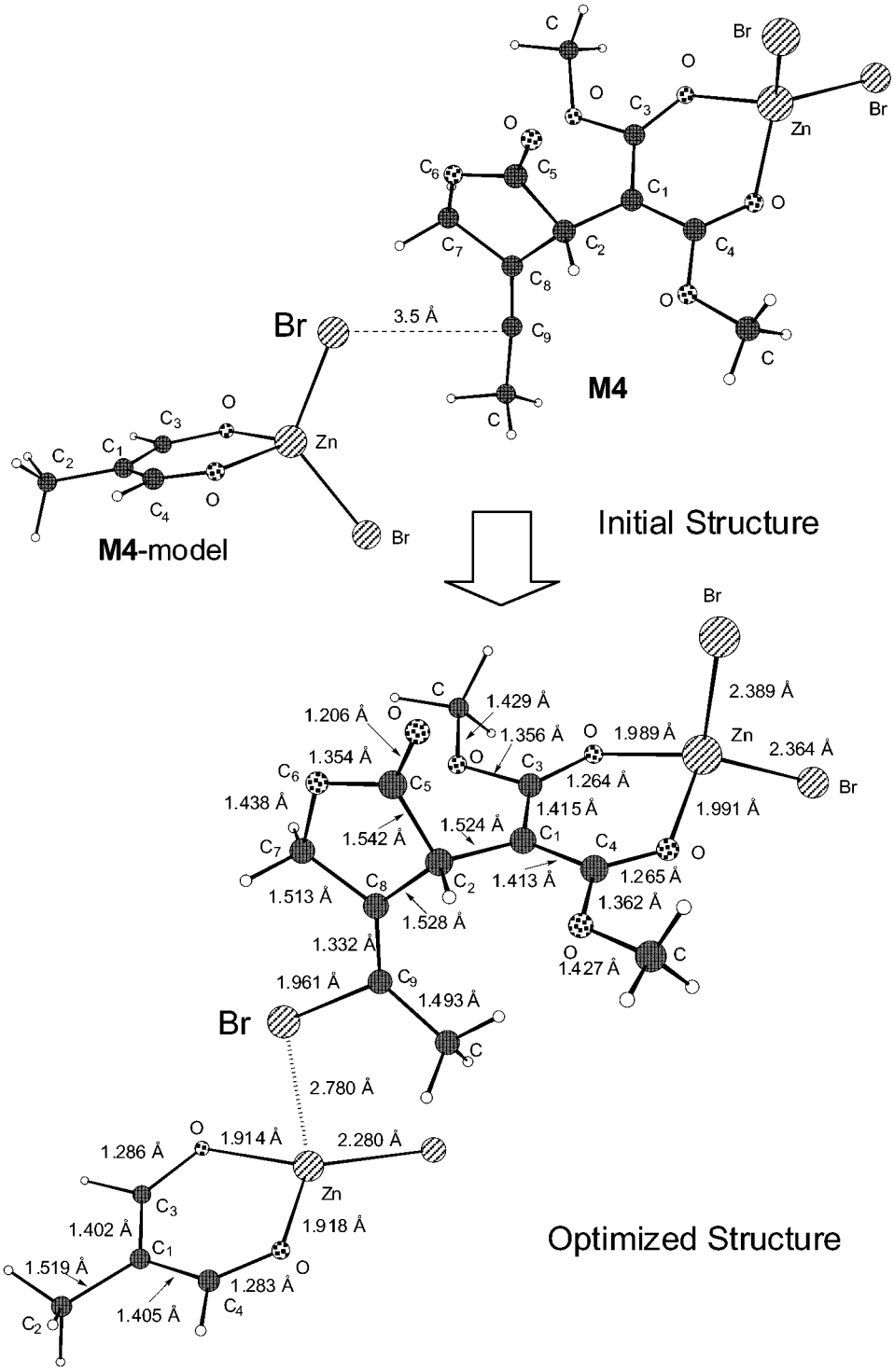
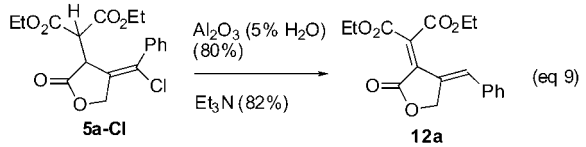


Figure 3. (top view) Initial structure for the geometry optimization. (bottom view) B3LYP/6-31G* SCRF-optimized structure.

(eq 2).[7] In addition, partial isomerization and/or dehydrohalogenation of cyclized products **5** and **8** by silica gel column chromatography leading to dienes was also observed. After extensive examination of the reaction conditions in this work, selective isomerization and dehydrohalogenation of cycloadducts **5** and **8** with Al_2O_3 and Et_3N have been established.

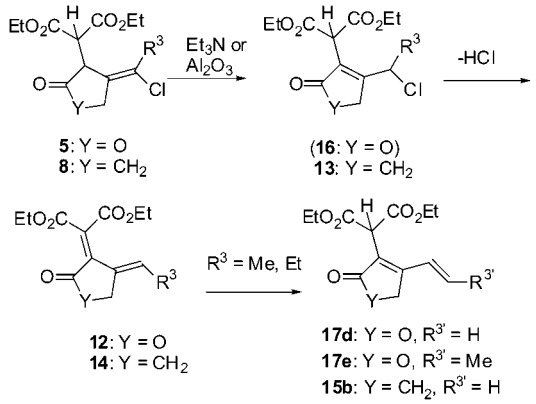
Typical examples are explained in detail. Treatment of the chlorolactone **5a-Cl** with Al_2O_3 and Et_3N gave **12a**[7] in 80% and 82% yields, respectively (eq 9). Compound **12a** was also obtained by the reaction of **1a** with $FeCl_3$ and workup by water, without purification by a reverse phase column, and subsequent Al_2O_3 column chromatography in 81% total yield. The yield is better than that



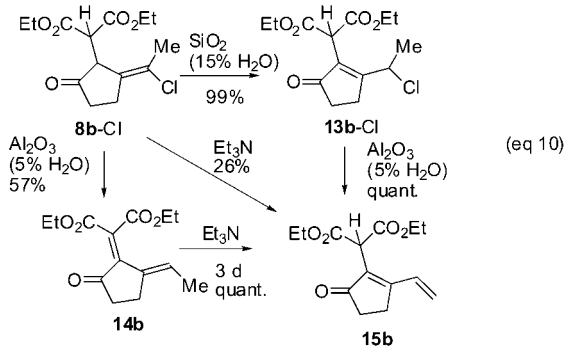
(eq 9)

with direct workup by Et_3N ($FeCl_3/Et_3N$, 66%; $ZnBr_2$–THF/Et_3N, 67%[7]). The cyclopentanone **8b-Cl** isomerizes to **13b-Cl** by silica gel (containing 15% H_2O) column

Scheme 2. Isomerization and Dehydrochlorination of Cyclized Products Obtained in Eqs 4, 5, and 8



chromatography. Column chromatography of **8b-Cl** with Al_2O_3 (containing 5% H_2O) gave the exomethylenic diene **14b** in 57% yield. Various transformations are shown in eq 10.

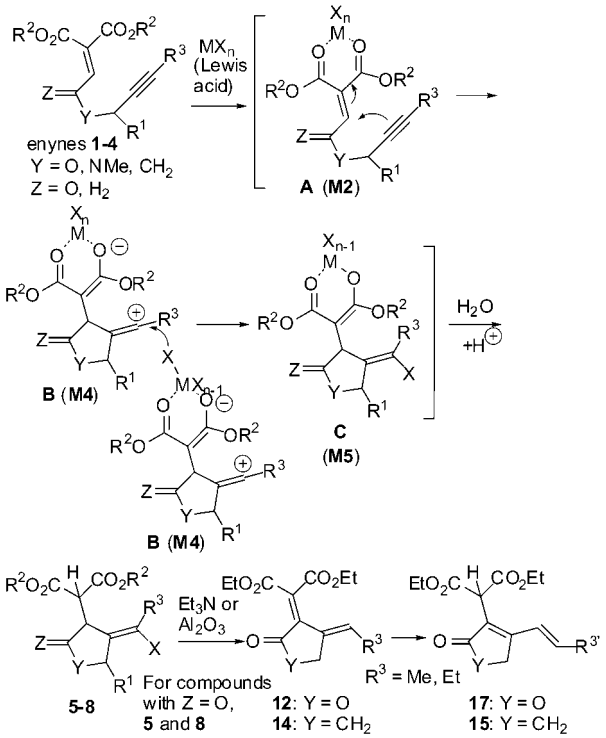


Other related reactions are included in Table 6 and Scheme 2. As shown in Scheme 2, the reaction may proceed through the isomerized chloro compound intermediates **13** (Y = CH_2) and **16** (Y = O), although chlorolactones **16** (Y = O) were not isolated. Dehydrochlorination of the chloro compounds gave the dialkylidene-γ-lactones **12** and dialkylidenecyclopentanone **14**. In the case of R^3 = Me, Et, the vinyl unsaturated-γ-lactones **17** and vinylcyclopentenone **15** were also obtained. Dialkylidene-γ-lactones **12** and cyclopentanone **14** should be the primary products in this process. Such isomerization of 1,2-dialkylidenecyclopentane to 1-vinylcyclopentenes by transition metals has also been reported.[6c,d] The diene **12a** is prevented from undergoing further isomerization due to the lack of a proton.

The cyclic diene **14a** (R^3 = Ph, see Scheme 2 for structure **14**) was not isolated, probably because of instability of the product. The structure of **12a** was confirmed by X-ray previously.[7] The olefin stereochemistries of **12**, **17**, and **14** were determined by the observed NOEs. The facile isomerization and dehydrochlorination is probably attributable to the acidity of the α-proton of the carbonyl group in the ring. Such isomerization and dehydrochlorination by treatment with Et_3N was not observed for γ-lactams **7** and cyclopentanes **6**.

Thus, the primary cycloadducts **5** and **8** may be transformed readily with bases (Al_2O_3 and Et_3N) to conjugated systems, dienes **12**, **17**, **14**, and **15**.

Scheme 3. Reaction Routes Forming the Five-Membered Rings and the Consequent Isomerization/Dehydrochlorination



V. Conclusions

A novel and general Lewis acid promoted enyne cyclization to give five-membered cyclic compounds has been discovered. The cyclization and subsequent isomerization/dehydrochlorination process is summarized in Scheme 3. Syntheses of diverse cyclic compounds, including heterocycles, by ring formation using transition-metal catalysts have been relatively limited.[18] Therefore, the present method should provide an efficient alternative to transition-metal-catalyzed cyclizations. Additionally, the cyclized products are highly substituted and are suitable for further elaboration (e.g. C−C bond formations). The usefulness of the combination of multiple bonds (i.e. electrophilic carbon−carbon double bond and the nucleophilic triple bond) in organic synthesis has been established in this study. The design of new substrates toward more diverse cyclic compounds and further transformation of the products to useful compounds are under investigation.

Experimental Section

General Methods. Melting points are uncorrected. IR spectra were recorded in the FT mode. ^{1}H NMR spectra were recorded at 400 MHz. ^{13}C NMR spectra were recorded at 100.6 MHz. Chemical shifts are reported in ppm relative to Me_4Si or residual nondeuterated solvent. ^{13}C mutiplicities were determined by DEPT and HSQC. Mass spectra were recorded at an ionizing voltage of 70 eV by EI. All reactions were carried out under a nitrogen atmosphere.

Preparation of Enyne Substrates 1a−e and 11. 1a,**b** were prepared by the reaction of diethyl or dimethyl ketoma-

(18) (a) Trost, B. M.; Edstrom, E. D.; Carter-Petillo, M. B. *J. Org. Chem.* **1989**, *54*, 4489. (b) Sturla, S. J.; Kablaoui, N. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 1976. (c) Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* **2000**, *2*, 3481. (d) Zhang, Q.; Lu, Z. *J. Am. Chem. Soc.* **2000**, *122*, 7604.

lonate with propargyl (triphenylphosphoranylidene)acetate and subsequent Sonogashira coupling[19] with iodobenzene.[7] **1c** was prepared by the reaction of diethyl ketomalonate with 2-but-3-ynyl (triphenylphosphoranylidene)acetate and subsequent Sonogashira coupling with iodobenzene.[7] **1d**,**e** were prepared by the reaction of diethyl ketomalonate with 1-but-2-ynyl and 1-pent-2-ynyl (triphenylphosphoranylidene)acetates. **11** was prepared by the reaction of diethyl ketomalonate with 1-but-3-ynyl (triphenylphosphoranylidene)acetate and subsequent Sonogashira coupling with iodobenzene.[7] These (triphenylphosphoranylidene)acetate esters were prepared by the reaction of the corresponding chloroacetates and triphenylphosphine in benzene and subsequent treatment with NaOH.[20] The chloroacetates were prepared 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.[7]

1,1-Diethyl 2-Propargyl Ethene-1,1,2-tricarboxylate. To an ice−water-cooled solution of diethyl ketomalonate (0.79 mL, 0.902 g, 5.18 mmol) in benzene (10.3 mL) was added propargyl (triphenylphosphoranylidene)acetate (1.856 g, 5.18 mmol). The mixture was warmed to room temperature and stirred for 5 h. The benzene was evaporated, and ether was added. The precipitate was removed by filtration. The filtrate was concentrated, and the residue was purified by column chromatography over silica gel with hexane−ether (1:2) as eluent to give the title compound (860 mg, 65%; R_f = 0.7): colorless crystals; mp 55−56 °C; ^{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), 2.52 (t, J = 2.4 Hz, 1H), 4.31 (q, J = 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 4.79 (d, J = 2.4, 2H), 6.89 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.99 (q), 14.04 (q), 53.14 (t), 62.34 (t), 62.72 (t), 75.85 (d), 76.64 (s), 128.80 (d), 140.02 (s), 162.12 (s), 162.83 (s), 164.03 (s); IR (KBr) 3272, 3084, 2992, 2968, 2948, 2136, 1730 cm^{-1}; MS (EI) m/z 254. Anal. Calcd for $C_{12}H_{14}O_6$: C, 56.69; H, 5.55. Found: C, 56.60; H, 5.51.

1d: yield 71%; R_f = 0.6 (hexane−ether 1:2); colorless crystals; mp 34−35 °C; ^{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), 1.86 (t, J = 2.4 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 4.75 (q, J = 2.4 Hz, 2H), 6.90 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 3.73 (q), 13.97 (q), 14.03 (q), 54.08 (t), 62.28 (t), 62.66 (t), 72.20 (s), 84.26 (s), 129.19 (d), 139.68 (s), 162.18 (s), 163.02 (s), 164.16 (s); IR (KBr) 2986, 2254, 1735, 1725, 1657 cm^{-1}; MS (EI) m/z 268; exact mass M$^+$ 268.0995 (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, 58.24; H, 5.98.

1e: yield 61%; R_f = 0.6 (hexane−ether 1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.5 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.36 (t, J = 7.1 Hz, 3H), 2.23 (qt, J = 7.5, 2.2 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.78 (t, J = 2.2 Hz, 2H), 6.90 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.49 (t), 13.50 (q), 13.95 (q), 14.00 (q), 54.09 (t), 62.24 (t), 62.62 (t), 72.35 (s), 89.93 (s), 129.25 (d), 139.63 (s), 162.18 (s), 163.00 (s), 164.13 (s); IR (neat) 2984, 2944, 2244, 1734, 1653 cm^{-1}; MS (EI) m/z 282; exact mass M$^+$ 282.1136 (calcd for $C_{14}H_{18}O_6$ 282.1103).

Typical Procedure for Preparation of 1a−c and 11. A mixture of 1,1-diethyl 2-propargyl ethene-1,1,2-tricarboxylate (763 mg, 3.0 mmol), iodobenzene (0.34 mL, 612 mg, 3.0 mmol), $PdCl_2(PPh_3)_2$ (42 mg, 0.06 mmol), and CuI (23 mg, 0.12 mmol) in Et_2NH (8.2 mL) was stirred at room temperature for 21 h. After removal of diethylamine under reduced pressure, water was added to the residue. The mixture was extracted with ether. The organic phase was washed with saturated aqueous NaCl, dried ($MgSO_4$), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane−ether (1:2) as eluent to give **1a** (615 mg, 62%).

1a: R_f = 0.6; 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), 4.31 (q, J = 7.1 Hz, 2H), 4.39 (q, J = 7.1 Hz, 2H), 5.02 (s, 2H), 6.93 (s, 1H), 7.30−7.35 (m, 3H), 7.44−7.46 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.98 (q), 14.03 (q), 54.08 (t), 62.31 (t), 62.68 (t), 81.87 (s), 87.39 (s), 121.92 (s), 128.42 (d), 129.04 (d), 129.07 (d), 131.97 (d), 139.83 (s), 162.17 (s), 162.99 (s), 164.10 (s); IR (neat) 2986, 2244, 1734, 1653 cm^{-1}; MS (EI) m/z 330; exact mass M$^+$ 330.1084 (calcd for $C_{18}H_{18}O_6$ 330.1103).

1b: yield 72%; R_f = 0.6 (hexane−ether 1:2); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.87 (s, 3H), 3.91 (s, 3H), 5.02 (s, 2H), 6.97 (s, 1H), 7.30−7.38 (m, 3H), 7.44−7.47 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 53.18 (q), 53.48 (q), 54.22 (t), 81.79 (s), 87.48 (s), 121.86 (s), 128.46 (d), 129.08 (d), 129.84 (d), 131.97 (d), 139.13 (s), 162.54 (s), 162.90 (s), 164.57 (s); IR (neat) 2958, 2238, 1734, 1653 cm^{-1}; MS (EI) m/z 302; exact mass M$^+$ 302.0798 (calcd for $C_{16}H_{14}O_6$ 302.0790).

1c: yield 53%; R_f = 0.7 (hexane−ether 1:2); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.62 (d, J = 6.6 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (qd, J = 7.1, 0.7 Hz, 2H), 5.76 (q, J = 6.6 Hz, 1H), 6.91 (s, 1H), 7.28−7.34 (m, 3H), 7.42−7.45 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.94 (q), 14.00 (q), 21.42 (q), 62.21 (t), 62.49 (d), 62.58 (t), 85.44 (s), 86.37 (s), 121.99 (s), 128.33 (d), 128.84 (d), 129.65 (d), 131.89 (d), 139.42 (s), 162.21 (s), 162.53 (s), 164.13 (s); IR (neat) 2988, 2238, 1729, 1647 cm^{-1}; MS (EI) m/z 344; exact mass M$^+$ 344.1272 (calcd for $C_{19}H_{20}O_6$ 344.1260).

11: yield 68%; R_f = 0.6 (hexane−ether 1:2); 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), 2.79 (t, J = 6.9 Hz, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.37 (t, J = 6.9 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 6.91 (s, 1H), 7.27−7.31 (m, 3H), 7.38−7.42 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.01 (q), 14.04 (q), 19.85 (t), 62.25 (t), 62.63 (t), 63.68 (t), 82.39 (s), 84.84 (s), 123.21 (s), 128.13 (d), 128.33 (d), 129.55 (d), 131.75 (d), 139.54 (s), 162.27 (s), 163.46 (s), 164.23 (s); IR (neat) 2986, 2362, 1729, 1653 cm^{-1}; MS (EI) m/z 344; exact mass M$^+$ 344.1285 (calcd for $C_{19}H_{20}O_6$ 344.1260). Anal. Calcd for $C_{19}H_{20}O_6$: C, 66.27; H, 5.85. Found: C, 66.12; H, 5.89.

Preparation of Enyne Substrate 2. A solution of $ClTi(OEt)_3$ (3.8 mL of 2 M solution in THF, 7.7 mmol)[21] and diethyl malonate (1.23 g, 7.7 mmol) was added to a solution of 6-phenyl-5-hexynal[6g] (1.3 g, 7.7 mmol) in THF (46 mL). To the mixture was added Et_3N (1.1 mL, 0.779 g, 7.7 mmol) at 0 °C, and the mixture was stirred for 1.5 h at room temperature. The reaction mixture was poured onto 4% aqueous HCl and extracted with ether and the extract washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was chromatographed on silica gel (hexane−ether 2:1) to afford **2** (808 mg, 34%).

2: R_f = 0.3 (hexane−ether 1:1); 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), 1.77−1.84 (m, 2H), 2.45−2.52 (m, 4H), 4.23 (q, J = 7.1 Hz, 2H), 4.28 (q, J = 7.1 Hz, 2H), 7.04 (t, J = 7.9 Hz, 1H), 7.26−7.30 (m, 3H), 7.37−7.40 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.18 (q), 14.22 (q), 19.16 (t), 27.47 (t), 28.96 (t), 61.39 (t), 81.54 (s), 88.99 (s), 123.75 (s), 127.76 (d), 128.27 (d), 129.41 (s), 131.60 (d), 148.25 (d), 163.98 (s), 165.51 (s); IR (neat) 2980, 1730, 1647 cm^{-1}; MS (EI) m/z 314 (17), 285 (43), 269 (30), 241 (100); exact mass M$^+$ 314.1541 (calcd for $C_{19}H_{22}O_4$ 314.1518).

Preparation of Enyne Substrates 3. To a solution of 1,1-diethyl 2-hydrogen ethenetricarboxylate (499 mg, 2.3 mmol) (prepared from 1,1-diethyl 2-*tert*-butyl ethenetricarboxylate upon treatment with CF_3CO_2H)[22] in THF (3.3 mL) were added *N*-methyl-*N*-(phenylpropargyl)amine[23] (670 mg, 4.6 mmol), HOBt (707 mg, 4.6 mmol), and WSC (1-[3-(dimethylamino)-propyl]-3-ethylcarbodiimide hydrochloride; 460 mg, 2.4 mmol) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C, warmed to room temperature, and stirred for 16 h. After

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removal of the solvent under reduced pressure, the residue was dissolved in CH_2Cl_2 and 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 with hexane−ether (1:2) as eluent to give **3a** (434 mg, 55%).

3a: R_f = 0.3 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 6:4) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 3.13 (s, 3 × 0.4H, minor rotamer), 3.19 (s, 3 × 0.6H, major rotamer), 4.28−4.36 (m, 4H + 2 × 0.4H), 4.51 (s, 2 × 0.6H), 7.29−7.35 and 7.41−7.44 (m, 6H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.99 (q), 14.08 (q), 32.99 (q), 34.82 (q), 36.80 (t), 40.81 (t), 61.95 (t), 61.99 (t), 62.31 (t), 82.29 (s), 82.95 (s), 84.40 (s), 85.56 (s), 121.99 (s), 122.46 (s), 126.88 (d), 128.38 (d), 128.46 (d), 128.61 (d), 128.74 (d), 128.89 (d), 131.82 (d), 134.18 (d), 134.56 (d), 134.71 (d), 162.97 (s), 163.00 (s), 163.81 (s), 164.07 (s), 164.24 (s), 164.29 (s); IR (neat) 2984, 2938, 1734, 1655 cm^{-1}; MS (EI) m/z 343; exact mass M$^+$ 343.1397 (calcd for $C_{18}H_{21}NO_5$ 343.1420).

Methyl(2-hexynyl)amine was prepared according to the procedure for methyl(phenylpropargyl)amine:[24] colorless oil; bp 30−40 °C/15 mmHg; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.982 (t, J = 7.4 Hz, 3H), 1.53 (qt, J = 7.2, 7.1 Hz, 2H), 1.60 (bs, 1H), 2.17 (tt, J = 7.1, 2.2 Hz, 2H), 2.46 (s, 3H), 3.36 (t, J = 2.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.54 (q), 20.76 (t), 22.35 (t), 35.30 (q), 40.44 (t), 78.02 (s), 83.71 (s); IR (neat) 3320, 2968, 2936, 2876, 2362 cm^{-1}; MS (EI) m/z 111.

3b: yield 48%; R_f = 0.3 (hexane−ether 1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) (2 rotamers, ratio 5.5:4.5) δ (ppm) 0.970 (t, J = 7.3 Hz, 3 × 0.55H, major rotamer), 0.973 (t, J = 7.3 Hz, 3 × 0.45H, minor rotamer), 1.32−1.34 (m, 6H), 1.47−1.57 (m, 2H), 2.13−2.19 (m, 2H), 3.04 (s, 3 × 0.45H), 3.11 (s, 3 × 0.55H), 4.07 (t, J = 2.3 Hz, 2 × 0.45H), 4.25 (t, J = 2.3 Hz, 2 × 0.55H), 4.27−4.36 (m, 4H), 7.32 (s, 1 × 0.55H), 7.36 (s, 1 × 0.45H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.53 (q), 13.56 (q), 13.99 (q), 14.10 (q), 20.67 (t), 20.73 (t), 21.97 (t), 22.08 (t), 32.85 (q), 34.56 (q), 36.42 (t), 40.43 (t), 61.88 (t), 61, 93 (t), 62.27 (t), 73.47 (s), 73.73 (s), 85.00 (s), 86.27 (s), 134.42 (t), 134.50 (t), 134.59 (s), 163.04 (s), 163.65 (s), 163.93 (s); IR (neat) 2974, 1734 cm^{-1}; MS (EI) m/z 309; exact mass M$^+$ 309.1554 (calcd for $C_{16}H_{23}NO_5$ 309.1576).

Preparation of Enyne Substrates 4a,b. 4a,**b** were prepared by the reaction of diethyl ketomalonate with carbonylmethylenetriphenylphosphoranes in the same manner as the preparation of 1,1-diethyl 2-propargyl ethene-1,1,2-tricarboxylate described above. The corresponding carbonylmethylenetriphenylphosphoranes were prepared from the reaction of acetomethylenetriphenylphosphorane, *n*-BuLi, and phenylpropargyl bromide[24] or 1-bromo-2-butyne, according to the literature procedure.[25]

4a: yield 41%; R_f = 0.6 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 2.73 (t-like, J = 7.3 Hz, 2H), 2,96 (t-like, J = 7.0 Hz, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.37 (q, J = 7.1 Hz, 2H), 7.18 (s, 1H), 7.27−7.29 (m, 3H), 7.37−7.39 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.80 (t), 13.92 (q), 14.02 (q), 42.73 (t), 62.19 (t), 62.60 (t), 81.47 (s), 87.72 (s), 123.40 (s), 127.93 (d), 128.27 (d), 131.63 (d), 134.81 (d), 135.88 (s), 162.69 (s), 164.63 (s), 196.57 (s); IR (neat) 2986, 1734, 1707, 1630 cm^{-1}; MS (EI) m/z 328.

4b: yield 53%; R_f = 0.6 (hexane−ether 1:2); pale yellow crystals; mp 28−29 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.32 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.75 (t, J = 2.6 Hz, 2H), 2.42−2.47 (m, 2H), 2.80−2.84 (m, 2H), 4.30 (q, J = 7.1 Hz, 2H), 4.45 (q, J = 7.1 Hz, 2H), 7.15 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 3.44 (q), 13.07 (t), 13.85 (q), 13.97 (q), 42.99 (t), 62.06 (t), 62.49 (t), 76.67 (s), 76.91 (s), 134.92 (d), 135.62 (s), 162.68 (s), 164.58 (s), 196.84 (s); IR (neat) 2986, 2924, 1736, 1700, 1630 cm^{-1}; MS (EI) m/z 266.

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Typical Cyclization Procedure (Table 1, Entry 1). To a solution of **1a** (122 mg, 0.37 mmol) in dichloromethane (0.8 mL) was added $ZnBr_2$ (96 mg, 0.43 mmol), followed by THF (30 μL, 27 mg, 0.37 mmol) at −78 °C. The mixture was warmed to −40 °C and stirred for 16 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 washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by reverse-phase column chromatography over Cosmosil 75C18-OPN with CH_3CN-H_2O (8:2) as eluent to give **5a-Br** (79 mg, 52%).

5a-Br: R_f = 0.5 (hexane−ether 1:2); colorless crystals; mp 126−127 °C (hexane−ether 1:2); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 3.17 (d, J = 4.5 Hz, 1H), 4.05 (ddd, J = 4.5, 2.2, 2.2 Hz, 1H), 4.12−4.27 (m, 4H), 4.90−4.91 (m, 2H), 7.34−7.37 (m, 2H), 7.38−7.46 (m, 3H) (selected NOEs are between δ 3.17 and 7.34−7.37 and δ 4.05 and 7.34−7.37); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.09 (q), 43.76 (d), 51.06 (d), 62.07 (t), 62.37 (t), 73.05 (t), 117.65 (s), 128.01 (d), 129.25 (d), 130.03 (d), 133.53 (s), 137.47 (s), 166.40 (s), 166.93 (s), 174.60 (s); IR (neat) 2980, 2936, 1789, 1744, 1721 cm^{-1}; MS (EI) m/z 412, 410; exact mass M$^+$ 412.0343 (calcd for $C_{18}H_{19}O_6{}^{81}Br$ 412.0344), M$^+$ 410.0334 (calcd for $C_{18}H_{19}O_6{}^{79}Br$ 410.0365).

5a-Cl: yield 98%, Table 1, entry 2; R_f = 0.6 (hexane−ether 1:2)); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.23 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 3.25 (d, J = 4.4 Hz, 1H), 4.11−4.53 (m, 5H), 4.99 (dd, J = 14.6, 2.4 Hz, 1H), 5.02 (dd, J = 14.6, 2.0 Hz, 1H), 7.39−7.48 (m, 5H) (selected NOEs are between δ 3.25 and 7.39−7.48 and δ 4.11−4.53 and 7.39−7.48); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91 (q), 14.03 (q), 42.93 (d), 50.95 (d), 62.03 (t), 62.36 (t), 71.04 (t), 127.13 (s), 127.76 (d), 129.20 (d), 130.10 (d), 130.55 (s), 135.76 (s), 166.48 (s), 166.89 (s), 174.55 (s); IR (neat) 2986, 2942, 1792, 1740, 1734 cm^{-1}; MS (EI) m/z 368, 366; exact mass M$^+$ 366.0855 (calcd for $C_{18}H_{19}ClO_6$ 366.0870).

5b-Cl: yield 83%, Table 1, entry 3; R_f = 0.3 (hexane−ether 1:1)); colorless crystals (hexane−EtOAc 1:1); mp 133−135 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 3.29 (d, J = 4.4 Hz, 1H), 3.71 (s, 3H), 3.73 (s, 3H), 4.15 (ddd, J = 4.4, 2.3, 2.1 Hz, 1H), 5.00 (dd, J = 14.6, 2.3 Hz, 1H), 5.03 (dd, J = 14.6, 2.1 Hz, 1H), 7.38−7.48 (m, 5H) (selected NOEs are between δ 3.29 and 7.38−7.48 and δ 4.15 and 7.38−7.48); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 42.99 (d), 50.74 (d), 53.05 (q), 53.24 (q), 71.12 (t), 127.40 (s), 127.77 (d), 129.29 (d), 130.16 (d), 130.38 (s), 135.78 (s), 166.92 (s), 167.41 (s), 174.52 (s); IR (neat) 2956, 1787, 1750, 1729 cm^{-1}; MS (EI) m/z 338; exact mass M$^+$ 338.0519 (calcd for $C_{16}H_{15}ClO_6$ 338.0557). Anal. Calcd for $C_{16}H_{15}ClO_6$: C, 56.73; H, 4.46; Cl, 10.47. Found: C, 56.49; H, 4.33; Cl, 10.23. The NMR spectra were identical with those reported for a major isomer reported by Snider.[4a]

5c-Cl: yield 63%; diastereomer ratio 7:3, Table 1, entry 4; recrystallization of the diastereomer mixture with EtOAc gave a 9:1 diastereomer mixture (43% yield); R_f = 0.5 (hexane−ether 1:2); colorless crystals; mp 125−126 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.22 (t, J = 7.1 Hz, 3H), 1.23 (t, J = 7.1 Hz, 3H), 1.69 (d, J = 6.4 Hz, 3 × 0.9H, major diastereomer), 1.74 (d, J = 6.6 Hz, 3 × 0.1H, minor diastereomer), 3.07 (d, J = 4.2 Hz, 1 × 0.1H, minor), 3.15 (d, J = 4.4 Hz, 1 × 0.9H, major), 4.08−4.23 (m, 5H), 5.38 (qd, J = 6.4, 2.1 Hz, 1H), 7.35−7.38 (m, 2H), 7.42−7.45 (m, 3H) (selected NOEs are between δ 3.15 and 7.35−7.38 and δ 4.08−4.23 and 7.35−7.38); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.92 (q), 14.07 (q), 19.13 (major) (q), 18.63 (minor) (q), 43.29 (major) (d), 44.01 (minor) (d), 50.58 (major) (d), 51.09 (minor) (d), 61.82 (t), 62.32 (t), 79.02 (major) (d), 79.24 (minor) (d), 127.10 (s), 128.18 (major) (d), 127.77 (minor) (d), 129.12 (major) (d), 129.30 (minor) (d), 130.25 (major) (d), 129.93 (minor) (d), 135.32 (s), 136.41 (s), 166.67 (s), 166.85 (s), 173.53 (s); IR (neat) 2990, 2940, 1783, 1744, 1721 cm^{-1}; MS (EI) m/z 380; exact mass M$^+$ 380.1013 (calcd for $C_{19}H_{21}ClO_6$ 380.1027). Anal. Calcd for $C_{19}H_{21}ClO_6$: C, 59.92; H, 5.56; Cl, 9.31. Found: C, 59.57; H, 5.47; Cl, 9.10.

Typical Procedure (Table 2, Entry 3). To a solution of **1d** (109 mg, 0.41 mmol) in dichloromethane (0.7 mL) was

added $FeCl_3$ (75.8 mg, 0.47 mmol) at −78 °C. The mixture was warmed to room temperature and stirred for 16 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 washed with water, 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 **5d-Cl** (94 mg, 76%).

5d-Cl: R_f = 0.5 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.19 (dd, J = 1.9, 1.9 Hz, 3H), 3.89−3.92 (m, 1H), 3.95 (d, J = 4.4, 1H), 4.17−4.35 (m, 4H), 4.79 (ddq, J = 13.6, 2.3, 1.9 Hz, 1H), 4.87 (ddq, J = 13.6, 1.9, 1.7 Hz, 1H) (selected NOEs are between δ 2.19 and 3.89−3.92 and δ 2.19 and 3.95.; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.96 (q), 13.99 (q), 22.96 (q), 42.38 (d), 53.01 (d), 62.36 (t), 62.53 (t), 70.84 (t), 126.79 (s), 127.91 (s), 166.38 (s), 166.96 (S), 174.78 (S); IR (neat) 2986, 2944, 1783, 1734, 1653 cm^{-1}; MS (EI) m/z 306, 304; exact mass M^+ 304.0762 (calcd for $C_{13}H_{17}ClO_6$ 304.0714).

5d-Br: yield 39%, Table 2, entry 1; R_f = 0.6 (hexane−ether 1:2)): Pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.30 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.38 (ddd, J = 2.0, 2.0, 2.0 Hz, 3H), 3.87−3.90 (m, 1H), 3.97 (d, J = 4.4 Hz, 1H), 4.17−4.35 (m, 4H), 4.71 (dq, J = 13.7, 12.2, 2.0 Hz, 1H), 4.78 (dq, J = 13.7, 2.0, 1.8 Hz, 1H) (selected NOEs are between δ 2.38 and 3.87−3.90 and δ 2.38 and 3.97); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.96 (q), 13.97 (q), 25.39 (q), 43.03 (d), 52.87 (d), 54.39 (s), 62.28 (t), 62.36 (t), 62.53 (s), 62.62 (s), 72.90 (t), 117.57 (s), 130.71 (s), 166.30 (s), 166.92 (s), 174.85 (s); IR (neat) 2986, 2942, 1787, 1734 cm^{-1}; MS (EI) m/z 350, 348; exact mass M^+ 348.0205 (calcd for $C_{13}H_{17}O_6Br$ 348.0209).

9d: yield 16%, Table 2, entry 1; R_f = 0.4, hexane−ether (1:2); colorless crystals; mp 29−30 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.296 (t, J = 7.1 Hz, 3H), 1.302 (t, J = 7.1 Hz, 3H), 1.85 (t, J = 2.4 Hz, 3H), 3.54 (d, J = 7.1 Hz, 1H), 3.98 (d, J = 4.0 Hz, 1H), 4.21−4.33 (4H, m), 4.69−4.82 (3H, m); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 3.72 (q), 14.00 (q), 14.06 (q), 54.45 (t), 55.04 (d), 62.15 (t), 62.17 (t), 69.77 (d), 72.27 (s), 84.18 (s), 166.98 (s), 167.16 (s), 171.13 (s); IR (KBr) 3432, 2978, 2248, 1750−1709 cm^{-1}; MS (EI) m/z 286; exact mass M^+ 286.1012 (calcd for $C_{13}H_{18}O_7$ 286.1053).

5e-Br: yield 37%, Table 2, entry 4; R_f = 0.6 (hexane−ether 1:2); colorless crystals (hexane−ether 1:2); mp 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.17 (t, J = 7.4 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.42−2.61 (m, 2H), 3.89 (m, 1H), 3.91 (d, J = 4.4 Hz, 1H), 4.19−4.34 (m, 4H), 4.70 (dd, J = 13.6, 1.3 Hz, 1H), 4.77 (d, J = 13.6 Hz, 1H) (selected NOEs are between δ 2.42−2.61 and 3.89 and δ 2.42−2.61 and 3.91); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.26 (q), 14.00 (q), 14.03 (q), 31.34 (t), 43.06 (d), 53.55 (d), 62.33 (t), 62.59 (t), 72.84 (t), 125.80 (s), 129.90 (s), 166.27 (s), 166.93 (s), 174.75 (s); IR (neat) 2982, 2940, 1783, 1736 cm^{-1}; MS (EI) m/z 364, 362; exact mass M^+ 364.0388 (calcd for $C_{14}H_{19}O_6{}^{81}Br$ 364.0344), M^+ 362.0327 (calcd for $C_{14}H_{19}O_6{}^{79}Br$ 362.0365).

9e: yield, 29%, Table 2, entry 4; R_f = 0.4 (hexane−ether 1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.5 Hz, 3H), 1.295 (t, J = 7.1 Hz, 3H), 1.300 (t, J = 7.1 Hz, 3H), 2.22 (qt, J = 7.5, 2.2 Hz, 2H), 3.59 (d, J = 7.1 Hz, 1H), 3.97 (d, J = 4.0 Hz, 1H), 4.22−4.31 (m, 4H), 4.74 (dt, J = 15.0, 2.2 Hz), 4.77 (dd, J = 7.1, 4.0 Hz, 1H), 4.82 (dt, J = 15.0 2.2 Hz); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.42 (t), 13.44 (q), 13.95 (q), 13.99 (q), 54.39 (t), 55.04 (d), 62.04 (t), 62.06 (t), 69.70 (d), 72.38 (s), 89.79 (s), 166.89 (s), 167.07 (s), 171.06 (s); IR (neat) 3478, 2984, 2944, 2244, 1740, 1734 cm^{-1}; MS (EI) m/z 300; exact mass M^+ 300.1240 (calcd for $C_{14}H_{20}O_7$ 300.1209).

5e-Cl: yield 67%, Table 2, entry 5; R_f = 0.6 (hexane−ether 1:2); colorless crystals (hexane−ether 1:2); mp 164−165 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.17 (t, J = 7.4 Hz, 3H), 1.29 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.2 Hz, 3H), 2.32−2.50 (m, 2H), 3.89 (d, J = 4.6 Hz, 1H), 3.90−3.92 (m, 1H), 4.19−4.64 (m, 4H), 4.79 (ddt, J = 13.7, 1.6, 1.6 Hz, 1H), 4.87 (ddt, J = 13.7, 1.1, 1.1 Hz, 1H) (selected NOEs are between δ 2.32−2.50 and 3.89 and δ 2.32−2.50 and 3.90−3.92); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.31 (q), 14.04 (q), 29.43 (t), 42.31 (d), 53.65 (d), 62.34 (t), 62.61 (t), 70.79 (t), 127.15 (s), 133.15 (s), 166.36 (s), 166.96 (s), 174.72 (s); IR (neat) 2982, 2942, 1785, 1736 cm^{-1}; MS (EI) m/z 318, 320; exact mass M^+ 318.0898 (calcd for $C_{14}H_{19}ClO_6$ 318.0870). Anal. Calcd for $C_{14}H_{19}ClO_6$: C, 52.75; H, 6.01; Cl, 11.12. Found: C, 53.06; H 5.98; Cl, 10.99.

5e-I: yield 31%, Table 2, entry 6; R_f = 0.5 (hexane−ether 1:2); colorless crystals; mp 74−75 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (t, J = 7.4 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 1.32 (d, J = 7.1 Hz, 3H), 2.41−2.51 (m, 2H), 2.55−2.64 (m, 2H), 3.91−3.92 (m, 1H), 3.93 (d, J = 4.6 Hz, 1H), 4.16−4.38 (m, 4H), 4.60−4.62 (m, 2H) (selected NOEs are between δ 2.41−2.51 and 3.91−3.92, δ 2.55−2.64 and 3.91−3.92, δ 2.41−2.51 and 3.93, and δ 2.55−2.64 and 3.93); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.94 (q), 13.98 (q), 14.67 (q), 34.50 (t), 43.65 (d), 53.52 (d), 62.23 (t), 62.49 (t), 77.18 (t), 105.28 (s), 135.04 (s), 166.14 (s), 166.84 (s), 175.01 (s); IR (KBr) 2987, 2936, 1783, 1738 cm^{-1}; MS (EI) m/z 410; exact mass M^+ 410.0259 (calcd for $C_{14}H_{19}IO_6$ 410.0226). Anal. Calcd for $C_{14}H_{19}IO_6$: C 40.99; H, 4.67. Found: C, 40.76; H, 4.52.

Typical Cyclization Procedure (Table 4, Entry 1). To a solution of **3a** (294 mg, 0.86 mmol) in dichloromethane (1.9 mL) was added $ZnBr_2$ (223 mg, 0.99 mmol), followed by THF (70 μL, 62 mg, 0.86 mmol), at −78 °C. The mixture was warmed to −40 °C and stirred for 16 h. The reaction mixture was quenched by triethylamine (0.21 mL, 154 mg, 1.52 mmol) and then saturated aqueous $NaHCO_3$. The mixture was extracted with dichloromethane, and the organic phase was washed with water, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane−ether as eluent to give **7a-Br** (264 mg, 84%).

7a-Br: R_f = 0.3 (ether); pale yellow crystals; mp 108−110 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.226 (t, J = 7.1 Hz, 3H), 1.228 (t, J = 7.1 Hz, 3H), 2.98 (d, J = 0.7 Hz, 3H), 3.08 (d, J = 4.6 Hz, 1H), 3.96−3.97 (m, 1H), 4.04 (dd, J = 15.3, 1.9 Hz, 1H), 4.09 (dd, J = 15.3, 1.9 Hz, 1H), 4.10−4.25 (m, 4H), 7.34−7.45 (m, 5H) (selected NOEs are between δ 3.08 and 7.34−7.45 and δ 3.96−3.97 and 7.34−7.45); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.96 (q), 14.19 (q), 29.56 (q), 45.75 (d), 50.77 (d), 56.81 (t), 61.43 (t), 61.93 (t), 118.33 (s), 128.15 (d), 129.07 (d), 129.65 (d), 132.70 (s), 138.25 (s), 167.36 (s), 171.61 (s); IR (neat) 2988, 2942, 2920, 1750, 1727, 1707 cm^{-1}; MS (EI) m/z 425, 423. Anal. Calcd for $C_{19}H_{22}BrNO_5$: C, 53.79; H, 5.23; N, 3.30; Br, 18.85. Found: C, 53.74; H, 5.15; N, 3.34; Br, 18.83.

6E-Br: yield 64%, Table 3, entry 1; R_f = 0.6 (hexane−ether 1:1); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.60−1.72 (m, 1H), 1.82−1.91 (m, 5H), 2.01−2.15 (m, 2H), 2.53 (dddd, J = 17.3, 9.9, 7.6, 2.3 Hz, 1H), 2.69 (ddd, J = 17.3, 7.9, 3.7 Hz, 1H), 3.06 (d, J = 5.7 Hz, 1H), 3.42 (dddd, J = 7.7, 7.7, 5.7, 2.3 Hz, 1H), 3.92−4.08 (m, 2H), 4.09−4.17 (m, 2H), 7.27−7.37 (m, 5H) (selected NOEs are between δ 3.06 and 7.27−7.37 and δ 3.42 and 7.27−7.37); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.04 (q), 14.21 (q), 23.87 (t), 30.88 (t), 38.01 (t), 42.70 (d), 52.20 (d), 60.99 (t), 61.31 (t), 115.21 (s), 128.53 (d), 128.62 (d), 128.87 (d), 140.32 (s), 145.79 (s), 168.15 (s), 168.59 (s); IR (neat) 2968, 1734 cm^{-1}; MS (EI) m/z 394; exact mass 394.0806 (calcd for $C_{19}H_{23}O_4Br$ 394.0780).

6E-Cl: yield 46%, Table 3, entry 4; R_f = 0.6 (hexane−ether 1:1); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.14 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.1 Hz, 3H), 1.60−1.71 (m, 1H), 1.82−1.91 (m, 1H), 1.97−2.12 (m, 2H), 2.54 (dddd, J = 17.2, 9.3, 8.3, 2.3 Hz, 1H), 2.73 (ddd, J = 17.2, 7.7, 3.5 Hz, 1H), 3.10 (d, J = 5.7 Hz, 1H), 3.50 (dddd, J = 7.2, 7.2, 5.7, 2.3 Hz, 1H), 3.91−4.15 (m, 4H), 7.30−7.38 (m, 5H) (selected NOEs are between δ 3.10 and 7.30−7.38 and δ 3.50 and 7.30−7.38); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.02 (q), 14.16 (q), 23.87 (t), 30.60 (t), 34.96 (t), 42.32 (d), 52.28 (d), 60.96 (t), 61.30 (t), 124.44 (s), 128.59 (d), 128.68 (d), 138.70 (s), 142.79 (s), 168.16 (s), 168.65 (s); IR (neat) 2982, 1734 cm^{-1}; MS (EI) m/z 350; exact mass M^+ 350.1311 (calcd for $C_{19}H_{23}ClO_4$ 350.1285).

6Z-Cl (as a 8:2 mixture with **6E-Cl**): yield 23%, Table 3, entry 5; R_f = 0.6 (hexane−ether 1:1); 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), 1.41−1.53 (m, 1H), 1.79−1.88 (m, 1H), 1.97−

2.11 (m, 2H), 2.33 (ddd, J = 15.3, 7.3, 2.2 Hz, 1H),. 2.48−2.57 (m, 1H), 3.55 (dddd, J = 7.7, 7.7, 5.7, 2.2 Hz, 1H), 4.17−4.27 (m, 4H), 4.35 (d, J = 5.7 Hz, 1H), 7.27−7.40 (m, 5H) (selected NOEs are between δ 2.33 and 7.27−7.40 and δ 2.48−2.55 and 7.27−7.40); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.20 (q), 14.25 (q), 25.51 (t), 28.86 (t), 34.33 (t), 43.87 (d), 52.39 (d), 61.15 (t), 61.49 (t), 124.34 (s), 128.04 (d), 128.16 (d), 128.67 (d), 139.12 (s), 143.10 (s), 168.78 (s), 169.13 (s); IR (neat) 2966, 1734 cm^{-1}; MS (EI) m/z 350; exact mass M$^+$ 350.1262 (calcd for $C_{19}H_{23}ClO_4$ 350.1285).

7a-Cl: yield 64%, Table 4, entry 4; R_f = 0.3 (ether); pale yellow crystals; mp 94−95 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (t, J = 7.1 Hz, 3H), 1.24 (t, J = 7.2 Hz, 3H), 2.99 (d, J = 0.7 Hz, 3H), 3.15 (d, J = 4.6 Hz, 1H), 4.04−4.06 (m, 1H), 4.07−4.26 (m, 6H), 7.38−7.46 (m, 5H) (selected NOEs are between δ 3.15 and 7.38−7.46 and δ 4.04−4.06 and 7.38−7.46); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.00 (q), 14.17 (q), 29.60 (q), 45.09 (d), 50.76 (d), 54.48 (t), 61.42 (t), 61.96 (t), 127.51 (s), 127.99 (d), 129.08 (d), 129.72 (d), 129.72 (d), 129.75 (s), 136.63 (s), 167.37 (s), 171.54 (s); IR (neat) 2988, 1752, 1725, 1709 cm^{-1}; MS (EI) m/z 379; exact mass M$^+$ 379.1207 (calcd for $C_{19}H_{22}ClNO_5$). Anal. Calcd for $C_{19}H_{22}ClNO_5$: C, 60.08; H, 5.84; N, 3.69; Cl, 9.33. Found: C, 59.81; H, 5.74; N, 3.68; Cl, 9.51.

7a-I: yield 62%, Table 4, entry 5; R_f = 0.3 (ether); pale yellow crystals; mp 91−92 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.21 (t, J = 7.1 Hz, 3H), 1.25 (t, J = 7.1 Hz, 3H), 2.99 (d, J = 0.5 Hz, 3H), 3.03 (d, J = 4.6 Hz, 1H), 3.95−3.96 (m, 3H), 4.07−4.23 (m, 4H), 7.28−7.41 (m, 5H) (selected NOEs are between δ 3.03 and 7.28−7.41 and δ 3.95−3.96 and 7.28−7.41); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.95 (q), 14.26 (q), 29.52 (q), 46.22 (d), 50.92 (d), 61.43 (t), 61.52 (t), 61.90 (t), 95.21 (s), 127.77 (d), 129.06 (d), 129.24 (d), 138.58 (s), 141.61 (s), 167.30 (s), 167.40 (s), 172.01 (s); IR (neat) 2986, 2918, 1748, 1725, 1705 cm^{-1}; MS (EI) m/z 471; exact mass M$^+$ 471.0508 (calcd for $C_{19}H_{22}INO_5$ 471.0543). Anal. Calcd for $C_{19}H_{22}INO_5$: C 48.42; H, 4.71; N, 2.97; I, 26.93. Found: C, 48.50; H, 4.58; N, 3.01; I, 26.49.

7b-Br: yield 74%, Table 4, entry 6; R_f = 0.4 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.95 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.47−1.62 (m, 1H), 1.64−1.76 (m, 1H), 2.38−2.53 (m, 2H), 2.93 (d, J = 0.5 Hz, 3H), 3.79 (bd, J = 4.5 Hz, 1H), 3.85 (d, J = 4.5 Hz, 1H), 3.85 (dd. J = 14.3, 1.5 Hz, 1H), 3.95 (dd. J = 14.3, 1.1 Hz, 1H), 4.13−4.36 (m, 4H) (selected NOEs are between δ 2.38−2.53 and 3.79 and δ 2.38−2.53 and 3.85); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.16 (q), 14.02 (q), 14.06 (q), 21.70 (t), 29.51 (q), 39.27 (t), 45.16 (d), 53.26 (d), 56.48 (t), 61.66 (t), 62.09 (t), 125.17 (s), 129.51 (s), 167.18 (s), 167.32 (s), 171.67 (s); IR (KBr) 2968, 1745, 1734, 1715 cm^{-1}; MS (EI) m/z 391, 389; exact mass M$^+$ 389.0859 (calcd for $C_{16}H_{24}BrNO_5$ 389.0838).

7b-Cl: yield 69%, Table 4, entry 7; R_f = 0.5 (ether); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.95 (t, J = 7.4 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 1.47−1.75 (m, 2H), 2.29−2.42 (m, 2H), 2.93 (s, 3H), 3.81 (bd, J = 4.5 Hz, 1H), 3.84 (d, J = 4.5 Hz, 1H), 3.91 (dd, J = 14.3, 1.4 Hz, 1H), 4.01 (dd. J = 14.3, 0.9 Hz, 1H), 4.13−4.36 (m, 4H) (selected NOEs are between δ 2.29−2.42 and 3.81); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.30 (q), 14.04 (q), 14.07 (q), 20.69 (t), 29.57 (q), 37.42 (t), 44.52 (d), 53.36 (d), 53.98 (t), 61.66 (t), 62.08 (t), 126.68 (s), 132.06 (s), 167.25 (s), 167.38 (s), 171.64 (s); IR (neat) 2920, 1740, 1734, 1710 cm^{-1}; MS (EI) m/z 345; exact mass M$^+$ 345.1329 (calcd for $C_{16}H_{24}ClNO_5$ 345.1343).

7b-I: yield 49%, Table 4, entry 9; R_f = 0.5 (ether); colorless crystals; mp 65−66 °C (hexane−ether 1:1); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 0.96 (t, J = 7.3 Hz, 3H), 1.26 (t, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 1.43−1.57 (m, 1H), 1.61−1.74 (m, 1H), 2.37−2.53 (m, 2H), 2.93 (s, 3H), 3.76−3.84 (m, 3H), 3.88 (d, J = 4.6 Hz, 1H), 4.13−4.36 (m, 4H) (selected NOEs are between δ 2.37−2.53 and 3.76−3.84 and δ 2.37−2.53 and 3.88); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.93 (q), 14.02 (q), 14.09 (q), 23.34 (t), 29.46 (q), 42.32 (t), 45.64 (d), 53.28 (d), 61.46 (t), 61.65 (t), 62.09 (t), 105.48 (s), 134.94 (s), 167.10 (s), 167.27 (s), 172.01 (s); IR (KBr) 2980, 1731, 1705 cm^{-1}; MS (EI) m/z 437; exact mass M$^+$ 437.0705 (calcd for $C_{16}H_{24}INO_5$ 437.0699). Anal. Calcd for $C_{16}H_{24}INO_5$: C, 43.95; H, 5.53; N, 3.20. Found: C, 43.72; H, 5.59; N, 3.20.

8a-Cl: yield 68%, Table 5, entry 1; purified by Cosmosil 75C18PREP (CH_3CN-H_2O = 7:3); R_f = 0.6 (SiO_2, hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.217 (t, J = 7.1 Hz, 3H), 1.221 (t, J = 7.1 Hz, 3H), 2.51−2.59 (m, 1H), 2.70−2.78 (m, 1H), 2.84−3.02 (m, 2H), 3.12 (d, J = 4.6 Hz, 1H), 3.80 (bs, 1H), 7.33−7.43 (m, 5H) (selected NOEs are between δ 3.80 and 7.33−7.43); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91 (q), 14.10 (q), 28.90 (t), 36.88 (t), 50.16 (d), 53.09 (d), 61.73 (t), 61.88 (t), 128.12 (d), 129.03 (d), 129.33 (d), 136.72 (s), 137.67 (s), 167.69 (s), 167.74 (s), 215.14 (s).

8a-Cl in $CDCl_3$ solution isomerized to **13a-Cl** (R^3 = Ph in Scheme 2) after 1 day, in quantitative yield.[26]

13a-Cl: R_f = 0.6 (SiO_2, hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.0 Hz, 3H), 1.30 (t, J = 7.1 Hz, 3H), 2.38−2.57 (m, 3H), 2.92−3.01 (m, 1H), 4.07−4.33 (m, 4H), 4.84 (s, 1H), 6.40 (s, 1H), 7.32−7.41 (m, 3H), 7.56−7.59 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.05 (q), 25.38 (t), 33.37 (t), 47.02 (d), 57.81 (d), 62.36 (t), 62.56 (t), 127.68 (d), 128.68 (d), 128.69 (d), 132.75 (s), 136.76 (s), 167.19 (s), 172.48 (s), 206.81 (s); IR (neat) 2986, 1940, 1745, 1734, 1715, 1644 cm^{-1}; MS (EI) m/z 364, 366; exact mass 364.1094 (calcd for $C_{19}H_{21}ClO_5$ 364.1078).

8b-Cl: yield 59%, Table 5, entry 2; purified by Cosmosil 75C18OPN (CH_3CN-H_2O = 3:2); R_f = 0.2 (silica gel, hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.16 (bs, 3H), 2.35−2.46 (m, 1H), 2.59−2.73 (m, 2H), 2.85−2.94 (m, 1H), 3.57−3.59 (m, 1H), 3.84 (d, J = 4.4 Hz, 1H), 4.12−4.33 (m, 4H) (selected NOEs are between δ 2.16 and 3.57−3.59 and δ 2.16 and 3.84); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.02 (q), 23.22 (q), 28.25 (t), 37.98 (t), 49.35 (d), 54.84 (d), 62.05 (t), 62.17 (t), 127.20 (s), 133.68 (s), 167.55 (s), 7.73 (s), 215.65 (s); IR (neat) 2986, 2938, 1745, 1734, 1715, 1647 cm^{-1}; MS (EI) m/z 302, 304; exact mass 302.0948 (calcd for $C_{14}H_{19}O_5Cl$ 302.0921).

8b-Br: yield 47%, Table 5, entry 3); purified by silica gel (hexane−ether 1:2); R_f = 0.2 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.27 (t, J = 7.1 Hz, 3H), 1.31 (t, J = 7.1 Hz, 3H), 2.36 (ddd, J = 1.3, 1.3, 1.3 Hz, 3H), 2.36−2.47 (m, 1H), 2.56−2.73 (m, 2H), 2.79−2.86 (m, 1H), 3.55−3.58 (m, 1H), 3.85 (d, J = 4.6 Hz, 1H), 4.12−4.33 (m, 4H) (selected NOEs are between δ 2.36 and 3.55−3.58 and δ 2.36 and 3.85); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.00 (q), 25.77 (q), 31.28 (t), 38.19 (t), 49.83 (d), 54.72 (d), 62.05 (t), 62.17 (t), 118.96 (s), 136.62 (s), 167.45 (s), 167.68 (s), 215.65 (s); IR (neat) 2984, 2938, 1750, 1734, 1640 cm^{-1}; MS (EI) m/z 346, 348; exact mass 346.0453 (calcd for $C_{14}H_{19}BrO_5$ 346.0416).

10b: yield 13%, Table 5, entry 3; R_f = 0.5 (hexane−ether 1:2); 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), 2.71 (t, J = 7.4 Hz, 3H), 2.97−3.11 (m, 2H), 3.99 (d, J = 7.7 Hz, 1H), 4.07 (d, J = 3.5 Hz, 1H), 4.18−4.32 (m, 4H), 4.58 (dd, J = 7.7, 3.5 Hz, 1H), 7.26−7.29 (m, 3H), 7.37−7.39 (m, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.71 (t), 14.01 (q), 14.08 (q), 38.08 (t), 54.26 (d), 62.25 (t), 62.31 (t), 76.17 (d), 81.08 (s), 88.36 (s), 123.61 (s), 127.83 (d), 128.26 (d), 131.64 (d), 167.91 (s); IR (neat) 3480, 2984, 2238, 1735, 1601 cm^{-1}; MS (EI) m/z 346; exact mass 346.1386 (calcd for $C_{19}H_{22}O_6$ 346.1416).

Conversion of 5a to 12a (in Eq 9). (A) Filtration of **5a** (132 mg, 0.36 mmol) on 35 g of Al_2O_3 containing 5% H_2O by column (2.3 × 10 cm) with hexane−ether (1:1) as eluent yielded **12a** (94 mg, 80%).

(B) To a solution of **5a** (128 mg, 0.35 mmol) in dichloromethane (2.4 mL) was added triethylamine (86 μL, 63 mg, 0.62 mmol) at room temperature. The mixture was stirred for 1 h. The reaction mixture was concentrated in vacuo. The

(26) Compounds **12e**, **14b**, and **13b-Cl** could not be completely purified due to the lability to column packing. NMR spectra of pure compounds **8a-Cl** and **3a** could not be obtained due to the lability in $CDCl_3$ solution. Nevertheless, the major peaks in the NMR spectra agree with the structures.

residue was extracted with dichloromethane, and the organic phase was washed with saturated aqueous $NaHCO_3$, dried (Na_2SO_4), and evaporated in vacuo. The residue was purified by column chromatography over silica gel with hexane−ether as eluent to give **12a** (95 mg, 82%).

12a:[7] R_f = 0.4, hexane−ether (1:1); yellow crystals; mp 98−99 °C (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.34 (t, J = 7.1 Hz, 3H), 1.37 (t, J = 7.1 Hz, 3H), 4.35 (q, J = 7.1 Hz, 2H), 4.41 (q, J = 7.1 Hz, 2H), 5.18 (d, J = 2.4 Hz, 2H), 7.25−7.28 (m, 2H), 7.39−7.46 (m, 3H) and 8.15 (t, J = 2.4 Hz, 1H) (selected NOEs in the 2D-NOESY spectra were between δ 8.15 and 7.25−7.28 and δ 5.18 and 7.25−7.28); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.90 (q), 14.00 (q), 62.47 (t), 62.48 (t), 69.89 (t), 128.27 (s), 129.12 (d), 129.78 (s), 129.84 (d), 132.20 (s), 134.93 (s), 136.88 (d), 163.03 (s), 164.75 (s) and 167.85 (s); IR (KBr) 2984, 1775, 1738, 1700 cm^{-1}; MS (EI) m/z 330; exact mass M$^+$ 330.1090 (calcd for $C_{18}H_{18}O_6$ 330.1103). Anal. Calcd for $C_{18}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.27; H, 5.38.

Filtration of **8b-Cl** (70 mg, 0.23 mmol) on SiO_2 containing 15% H_2O by column chromatography (2.3 × 10 cm) with hexane−ether (1:1) as eluent yielded **13b-Cl** (in eq 10) (69 mg, ca. 99%).[26]

13b-Cl: R_f = 0.6 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.0 Hz, 3H), 1.28 (t, J = 7.1 Hz, 3H), 1.73 (d, J = 6.7 Hz, 3H), 2.15−2.54 (m, 2H), 2.70 (ddd, J = 18.6, 6.1, 3.7 Hz, 1H), 2.98 (ddd, J = 18.6, 6.0, 3.8 Hz, 1H), 4.15−4.31 (m, 4H), 4.75 (s, 1H), 5.32 (s, 1H), 5.32 (q, J = 6.7 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.03 (q), 14.08 (q), 22.69 (q), 24.22 (t), 33.29 (t), 46.74 (d), 52.80 (d), 62.34 (t), 62.52 (t), 131.79 (s), 167.21 (s), 167.24 (s), 174.74 (s), 206.82 (s); IR (neat) 2986, 2938, 1734, 1715, 1647 cm^{-1}; MS (EI) m/z 302; exact mass 302.0893 (calcd for $C_{14}H_{19}ClO_5$ 302.0921).

Column chromatography of **5d-Cl** and **5e-Cl** by Al_2O_3 gave **12d** (R^3 = Me, Scheme 2) and **12e** (R^3 = Et), respectively.

12d: yield 50%; R_f = 0.4 (hexane−ether 1:2); 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), 1.86 (dt, J = 7.6, 1.4 Hz, 3H), 4.30 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.91 (dq, J = 2.6, 1.4 Hz, 2H), 7.52 (qt, J = 7.6, 2.6 Hz, 1H) (selected NOEs are between δ 1.86 and 4.91); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.90 (q), 13.97 (q), 15.42 (q), 62.32 (t), 62.34 (t), 68.83 (t), 128.87 (s), 129.47 (s), 131.01 (s), 135.81 (d), 163.03 (s), 164.98 (s), 168.87 (s); IR (neat) 2988, 1765, 1748 cm^{-1}; MS (EI) m/z 268; exact mass 268.0974 (calcd for $C_{13}H_{16}O_6$ 268.0947).

12e: yield 77%; R_f = 0.4 (hexane−ether 1:2)); yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.12 (t, J = 7.5 Hz, 3H), 1.33 (t, J = 7.1 Hz, 3H), 1.35 (t, J = 7.1 Hz, 3H), 2.13−2.21 (m, 2H), 4.31 (q, J = 7.1 Hz, 2H), 4.38 (q, J = 7.1 Hz, 2H), 4.90 (ddd, J = 2.5, 1.2, 1.2 Hz, 2H), 7.39 (ddt, J = 7.7, 5.1, 2.5 Hz, 1H) (selected NOEs are between δ 2.13−2.21 and 4.90; ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 12.94 (q), 13.88 (q), 13.97 (q), 23.25 (t), 62.30 (t), 62.32 (t), 68.67 (t), 127.36 (s), 129.50 (s), 130.99 (s), 142.29 (d), 162.99 (s), 164.94 (s), 168.78 (s); IR (neat) 2984, 2944, 1770, 1750, 1734 cm^{-1}; MS (EI) m/z 282.

Treatment of **5d-Cl** and **5e-Cl** with Et_3N in CH_2Cl_2 gave **17d** (R^3 = Me, Scheme 2)[7] and **17e** (R^3 = Et), respectively.

17d: quantitative yield; R_f = 0.4 hexane−ether (1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) 1.29 (t, J = 7.1 Hz, 6H), 4.20−4.28 (m, 4H), 4.73 (s, 1H), 5.03 (s, 2H), 5.63 (d, J = 17.8 Hz, 1H), 5.65 (d, J = 11.0 Hz, 1H), 6.90 (dd, J = 17.8, 11.0 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) 14.08 (q), 48.21 (d), 62.55 (t), 69.56 (t), 119.60 (s), 123.55 (t), 127.55 (d), 158.01 (s), 166.55 (s), 173.39 (s); IR (neat) 2986, 1765−1734, 1659, 1601 cm^{-1}; MS (EI) m/z 268; exact mass M$^+$ 268.0954 (calcd for $C_{13}H_{16}O_6$ 268.0947).

17e: yield 80%; R_f = 0.4 (hexane−ether 1:2); pale yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.29 (t, J = 7.0 Hz, 6H), 1.94 (dd, J = 6.8, 1.6 Hz, 3H), 4.18−4.30 (m, 4H), 4.69 (s, 1H), 4.98 (s, 2H), 6.19 (dq. J = 16.1, 6.8 Hz, 1H), 6.58 (bd, J = 16.1 Hz, 1H) (selected NOEs are between δ 1.94 and 6.58 and δ 4.98 and 6.19); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.03 (q), 19.32 (q), 48.08 (d), 62.34 (t), 69.65 (t), 116.70 (s), 122.39 (d), 137.42 (d), 158.32 (s), 166.71 (s) 173.65 (s); IR (neat) 2988, 2942, 1750, 1657 cm^{-1}; MS (EI) m/z 282; exact mass 282.1111 (calcd for $C_{14}H_{18}O_6$ 282.1103).

Column chromatography of **8b-Cl** with Al_2O_3 (containing 5% H_2O) gave **14b** (in eq 10) in 57% yield.

14b: R_f = 0.5 (hexane−ether 1:2); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.31 (t, J = 7.1 Hz, 3H), 1.34 (t, J = 7.1 Hz, 3H), 1.88 (dt, J = 7.2, 1.5 Hz, 3H), 2.49−2.53 (m, 2H), 2.66−2.70 (m, 2H), 4.29 (q, J = 7.1 Hz, 2H), 4.35 (q, J = 7,1 Hz, 2H), 6.38 (qt, J = 7.2, 2.5 Hz, 1H) (selected NOEs are between δ 1.88 and 2.66−2.70); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 13.91 (q), 13.99 (q), 15.36 (q), 23.69 (t), 35.95 (t), 62.06 (t), 125.20 (s), 133.58 (d), 134.62 (s), 140.23 (s), 164.15 (s), 166.07 (s), 205.71 (s); IR (neat) 2986, 2940, 1734 cm^{-1}; MS (EI) m/z 266; exact mass M$^+$ 266.1155 (calcd for $C_{14}H_{18}O_5$ 266.1154).

Column chromatography of **13b-Cl** with Al_2O_3 (containing 5% H_2O) gave **15b** (in eq 10) quantitatively. Treatment of **8b-Cl** with Et_3N in CH_2Cl_2 for 1 h and purification with column chromatography (SiO_2) gave **15b** in 26% yield. Treatment of **8b-Cl** with Et_3N in $CDCl_3$ for 3 days gave **15b** quantitatively.

15b: R_f = 0.2 (hexane−ether 1:2; colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 1.26 (t, J = 7.1 Hz, 6H), 2.50−2.53 (m, 2H), 2.81−2.83 (m, 2H), 4.15−4.27 (m, 4H), 4.76 (s, 1H), 5.62 (dd, J = 10.7, 0.9 Hz, 1H), 5.87 (dd, J = 17.4, 0.9 Hz, 1H), 7.03 (dd, J = 17.4, 10.8 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ (ppm) 14.10 (q), 25.72 (t), 33.14 (t), 47.13 (d), 62.09 (t), 123.48 (t), 131.60 (d), 132.75 (s), 167.53 (s), 168.09 (s), 206.73 (s); IR (neat) 2986, 2940, 1745, 1734, 1700, 1634 cm^{-1}; MS (EI) m/z 266; exact mass M$^+$ 266.1154 (calcd for $C_{14}H_{18}O_5$ 266.1154).

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Supporting Information Available: Figures giving B3LYP/6-31G* SCRF-optimized geometries of **M2I**, **M4**, **M5**, **M8**, **M9**, **M10** and **M1** and ^{1}H and ^{13}C NMR spectra for compounds **5a-Br**, **5d-Cl**, **6E-Cl**, **6E-Br** and **7b-Br**. This information is available free of charge via the Internet at http://pubs.acs.org.

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