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Diastereoselective Synthesis of Substituted Tetrahydrofurans via Prins Cyclization of Enol Ethers

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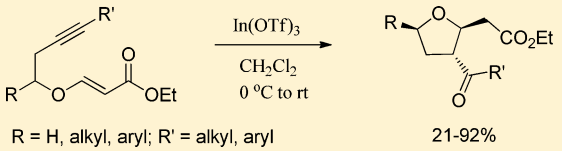
Supporting Information

ABSTRACT: Indium triflate can be efficiently used for Prins cyclization of acrylyl enol ethers to give tetrahydrofuran ring stereo- and regioselectively in good yields. The formation of five-membered rings is against the Baldwin's rule.



R = H, alkyl, aryl; R' = alkyl, aryl

21-92%

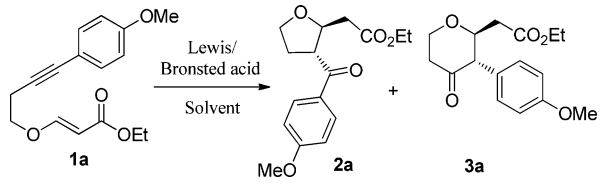
INTRODUCTION

The presence of saturated oxygen heterocycles in many naturally occurring and biologically active molecules including polyether antibiotics inspired chemists in the development of new methods for the synthesis of cyclic ethers.[1] They are also versatile synthetic building blocks in organic synthesis.[2] Numerous synthetic approaches have been developed for the preparation of tetrahydrofuran rings,[3] including radical cyclization of alkoxyacrylates.[4] These methods have their own merits and demerits, but some of them suffer from diastereoselectivity. Prins cyclization is an important reaction for the synthesis of tetrahydropyrans and tetrahydrofurans because of its diastereoselectivity.[5] Although there are many reported methods for the synthesis of di- and tetrahydropyrans via the Prins cyclization reaction, methods for the synthesis of tetrahydrofuran are limited.[5a−c,6] We now present a method for the stereoselective synthesis of *cis*-2,5-tetrahydrofurans using the Prins cyclization reaction of enol ethers having alkyne side chains mediated by indium triflate at ambient temperature in moderate to good yields.

RESULTS AND DISCUSSION

In continuation of our interest in oxygen heterocycles[7] we were in search of synthesizing multifunctional five-membered oxygen heterocyclic frameworks. Recently, we had developed a method for the synthesis of *cis*-2,6-dihydropyrans via the Prins cyclization of enol ether. The enol ethers having a terminal double bond were treated with trimethylsilyl trifluoromethanesulfonate (TMSOTf) to give *cis*-2,6-dihydropyrans.[8] In the present work an attempt was made to cyclize enol ethers having an alkyne group as a nucleophile. To start with, enol ether **1a** was treated with TMSOTf in dichloromethane at 0 °C to room temperature, but the reaction ended with a black material. Several Lewis and Bronsted acids were screened, and finally it was found that 0.2 equiv of indium triflate [$In(OTf)_3$] in dichloromethane gave some product in 40% yield. The product was characterized as ethyl 2-(3-(4-methoxybenzoyl)tetrahydrofuran-2-yl)acetate **2a** by NMR spectroscopy and mass spectrometry (Table 1). The yield was increased to 60% by increasing the amount of $In(OTf)_3$ to 0.5 equiv. Increasing the amount of reagent to 1.0 equiv also resulted in the same yield. It was observed that $Cu(OTf)_2$ and $BF_3{\cdot}Et_2O$ also resulted in the desired product but gave 28 and 35% yields, respectively. $Zn(OTf)_2$ was found to be unreactive. Brønsted acid TfOH gave two inseparable products, tetrahydrofuran **2a** and tetrahydropyranone **3a**, in 42% overall yield with a ratio of 1:3. On the other hand, camphorsulfonic acid (CSA) was found to be inefficient for the reaction. Similarly, $BF_3{\cdot}Et_2O$ in benzene produced tetrahydrofuran **2a** and tetrahydropyranone **3a** in 30% overall yield with a ratio of 5:1. On the other hand,

Table 1. Optimization of the Reaction



1a 2a 3a

entry	Lewis/Brønsted acid (equiv)	time (h)	solvent	% yield[a] 2 & 3
1	TMSOTf (1.1)	24	CH_2Cl_2	d[c]
2	$In(OTf)_3$ (0.2)	24	CH_2Cl_2	40 (**2**)
3	$In(OTf)_3$ (0.5)	12	CH_2Cl_2	60 (**2**)
4	$In(OTf)_3$ (1.0)	12	CH_2Cl_2	60 (**2**)
5	$BF_3{\cdot}Et_2O$ (1.1)	24	CH_2Cl_2	35 (**2**)
6	$BF_3{\cdot}Et_2O$ (1.1)	24	benzene	30 (**2** + **3**)[b]
7	TfOH (1.1)	24	CH_2Cl_2	42 (**2** + **3**)[b]
8	$CeCl_3{\cdot}7H_2O$	24	CH_2Cl_2	n[e]
9	$Cu(OTf)_2$ (0.2)	24	CH_2Cl_2	28 (**2**)
10	$Zn(OTf)_2$ (1)	30	CH_2Cl_2	n[e]
11	CSA (1)	10	CH_2Cl_2	n[e]
12	$FeCl_3$ (1)	2	CH_2Cl_2	45 (**2**)[d]
13	$InCl_3$ (1)	24	CH_2Cl_2	28 (**2**)

[a]Yields refer to isolated yield. The compounds were characterized by IR, NMR, and mass spectrometry. [b]Ratio is determined by ^1H NMR. [c]d = decomposed product. [d]Along with some decomposed products. [e]n = no reaction.

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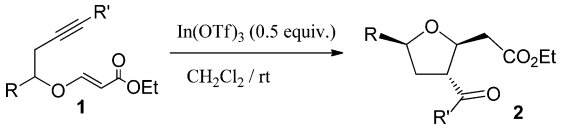
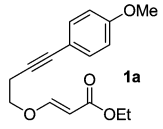
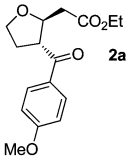
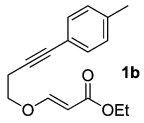
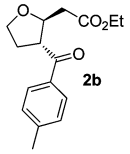
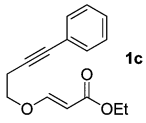
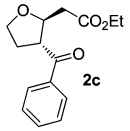
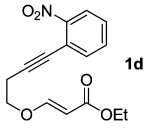
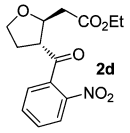
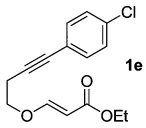
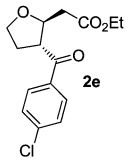
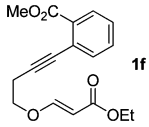
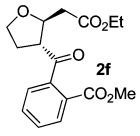
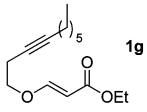
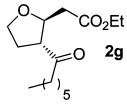
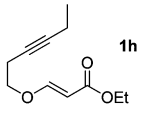
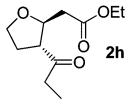
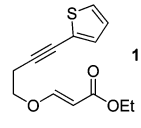
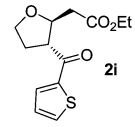
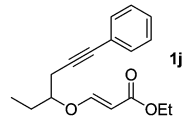
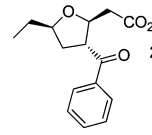
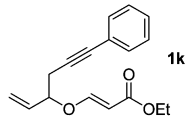
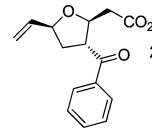
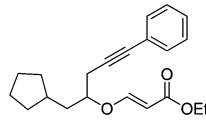
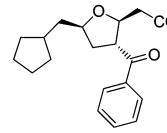
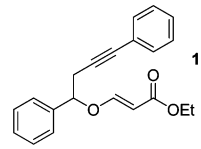
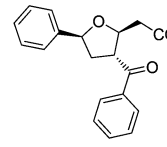
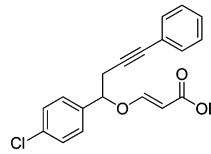
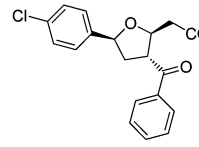
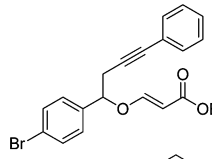
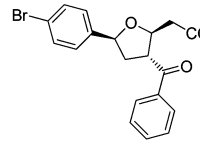
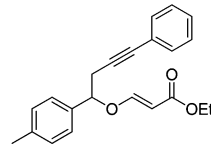
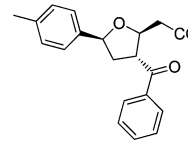
Table 2. In(OTf)$_3$-Mediated Cyclization of Alkyne Enol Ether



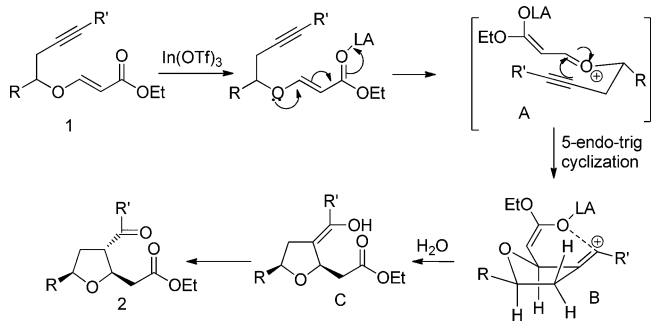
entry	acrylyl enol ether **1**	product **2**	(%)yield[a]
1			60
2			56
3			54
4			0[d]
5			45
6			0[d]
7			21
8			30
9			67
10			84
11			63
12			63
13			92
14			71
15			72
16			81

[a]Yield refers to isolated yield. The compounds are characterized by IR, ^{1}H, ^{13}C NMR, and mass spectrometry. d = decomposed product.

$CeCl_3·7H_2O$ was also found to be inefficient. The reaction with $FeCl_3$ was completed within 2 h producing **2a** in 45% yield along with some decomposed products. $InCl_3$ gave **2a** in 28%, and starting material **1a** was recovered in 50%.

Having obtained the optimized conditions, we further examined the scope of the reaction with a variety of substrates (Table 2). It was observed from Table 2 that ethers having aromatic-substituted alkyne side chains gave good to moderate yields. On the other hand, ethers with aliphatic-substituted alkynes (entries 7 and 8) gave low yields. Electron-withdrawing groups on the aromatic ring of the alkyne side chain play a role in the reactivity of the substrates. Electron-withdrawing groups on the aromatic ring reduce the reactivity of the substrate **1e** (entry 5). Substrates **1d** and **1f** having strong electron-withdrawing groups on the aromatic ring, such as $-NO_2$ and $-COOMe$ (entries 4 and 6), were decomposed under these reaction conditions. On the other hand, electron-donating groups on the

Scheme 1. Mechanism of the Reaction



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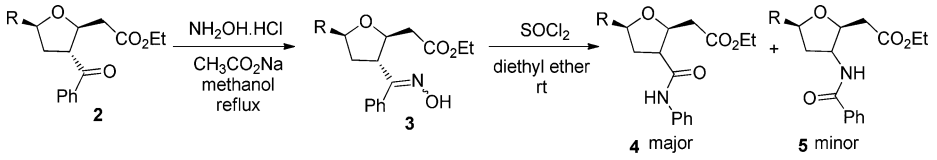
Scheme 2. Application of Beckmann Rearrangement in 3-Benzoyl Tetrahydrofuran



R = H; **2c**
R = Et; **2j**

R = H; **4c**:**5c** = 9:1 (50%)
R = Et; **4j**:**5j** = 10:0 (42%)

aromatic ring enhance the reactivity (entries 1 and 2). This might be due to the better stabilization of carbocation **B** (Scheme 1) by the electron-rich aromatic ring and destabilization of the same carbocation by the electron-deficient aromatic ring. Aliphatic-substituted substrates (entries 7 and 8) gave 21 and 30% yields, respectively, which indicate that carbocation **B** is less stabilized by alkyl groups than the electron-rich aromatic groups at the alkyne terminus. It was observed that 1-substituted enol ethers (entries 10−16) gave tetrahydrofuran in good yields.

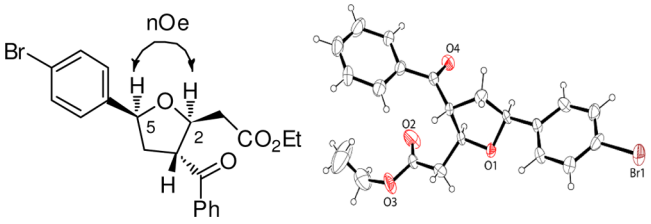


Figure 1. Correlation between NOE and X-ray crystallographic structure of **2o**.

Thiophene-substituted enol ether **1i** (entry 9) also worked well, giving a 67% yield. The stereochemistry of the product was determined by NOE of compound **2o**, which was further confirmed by X-ray crystallographic analysis.[9] There was a strong NOE between 2C−H and 5C−H protons, which indicates that substituents at 2 and 5 positions are *cis* to each other. The reaction is highly diastereoselective, which was determined from ^{1}H and ^{13}C NMR analysis of crude compounds.

The mechanism of the reaction can be explained as follows. The ester group of enol ether **1** is activated by $In(OTf)_3$ to form oxocarbenium ion **A**. The oxocarbenium ion **A** is then attacked by the alkyne group via a 5-endo-trig cyclization to give carbocation **B**. The formation of a five-membered ring is in contrast to Baldwin's rule,[10] but in the present situation the formation of a five-membered ring is possible because of proper alignment of the molecular orbital of the alkyne group with the sp^2-hybridized carbonyl group.[11] The intermediate carbocation **B** is stabilized by enolate,[6e,8] which is then trapped by water during the work up of the reaction to give enol **C**, which after rearrangement gives ketone **2** (Scheme 1).

In order to provide the synthetic application of 3-benzoyl tetrahydrofuran **2**, Beckmann rearrangement reaction was studied (Scheme 2). It was observed that Beckmann rearrangement of 3-benzoyl tetrahydrofuran **2c** resulted in an inseparable mixture of *N*-phenyltetrahydrofuran-3-carboxamide **4c** and *N*-(tetrahydrofuran-3-yl)benzamide **5c** with a ratio of 9:1 in 50% overall yield. On the other hand, **2j** gave only *N*-phenyl-tetrahydrofuran-3-carboxamide **4j** as a single isomer in 42% yield. In both the cases 40% of starting oximes were recovered. This indicates that the phenyl group is a better migrating group than the tetrahydrofuran ring.

CONCLUSIONS

In conclusion, we have developed a mild and efficient method for the synthesis of substituted tetrahydrofurans via Prins cyclization reaction from enol ethers in good yields. The method is highly diastereoselective and gives only *cis*-2,5-diastereomers. The 3-benzoyl tetrahydrofuran could be converted into *N*-phenyl-tetrahydrofuran-3-carboxamide in moderate yield.

EXPERIMENTAL SECTION

General Information. All the reagents were of reagent grade (AR grade) and were used as purchased without further purification. Silica gel (60−120 mesh size) was used for column chromatography. Reactions were monitored by TLC on silica gel GF_{254} (0.25 mm). Melting points were recorded in open capillary tubes and are uncorrected. Fourier transform-infrared (FT-IR) spectra were recorded as neat liquid or KBr pellets. NMR spectra were recorded in $CDCl_3$ with tetramethylsilane as the internal standard for ^{1}H (600 MHz, 400 MHz) or ^{13}C (150 MHz, 100 MHz) NMR. Chemical shifts (δ) are reported in parts per million, and spin−spin coupling constants (J) are given in Hz. HRMS spectra were recorded using a Q-TOF mass spectrometer.

General Procedure for the Preparation of Acrylyl Enol Ethers. To a solution of homopropargylic alcohol (2 mmol) in dichloromethane (3 mL), *N*-methyl morpholine (2 mmol) and ethyl propiolate (2.2 mmol) were added. The reaction mixture was stirred at room temperature, and the progress of the reaction was monitored by TLC. After completion of the reaction the solvent was removed on a rotary evaporator and diluted with water (5 mL). The product was extracted with ethyl acetate (3 × 10 mL), and the combined organic layers were washed with brine (3 mL) and finally dried over anhydrous Na_2SO_4. The solvent was removed under a rotary evaporator, and the crude product was purified on silica gel column chromatography using ethyl acetate and hexane as eluents.

*(E)-Ethyl 3-((4-(4-Methoxyphenyl)but-3-yn-1-yl)oxy)acrylate (**1a**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.66; yield 450 mg, 82%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H), 2.82 (t, J = 7.2 Hz, 2 H), 3.81 (s, 3 H), 4.03 (t, J = 7.2 Hz, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 12.4 Hz, 1 H), 6.82 (d, J = 9.2 Hz, 2 H), 7.34 (d, J = 8.4 Hz, 2 H), 7.63 (d, J = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.3, 55.2, 59.8, 69.1, 82.3, 97.1, 104.2, 113.9, 115, 133.1, 159.4, 162.0, 167.5; IR (KBr, neat) 2986, 2839, 1708, 1627, 1259, 1136, 1038, 765 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}O_4$ $(M + H)^+$ 275.1278, found 275.1279.

*(E)-Ethyl 3-((4-(p-Tolyl)but-3-yn-1-yl)oxy)acrylate (**1b**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.63; yield 454 mg, 88%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 2.34 (s, 3 H), 2.82 (t, J = 7.2 Hz, 2 H), 4.03 (t, J = 7.2 Hz, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 12.4 Hz, 1 H), 7.09 (d, J = 8.0 Hz, 2 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.63 (d, J = 12.4 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.4, 21.6, 60.0, 69.2, 82.7, 84.1, 97.3, 120.2, 129.2, 131.7, 138.3, 162.1, 167.8; IR (KBr, neat) 2975, 2929, 1709, 1626, 1135, 1044, 818, 745 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{19}O_3$ $(M + H)^+$ 259.1329, found 259.1320.

*(E)-Ethyl 3-((4-Phenylbut-3-yn-1-yl)oxy)acrylate (**1c**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.61; yield 410 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.82 (t, J = 7.2 Hz, 2 H), 4.03 (t, J = 7.2 Hz, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 12.6 Hz, 1 H), 7.28−7.30 (m, 3 H), 7.39−7.41 (m, 2 H), 7.62 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.5, 60.0, 69.2, 82.7, 85.0, 97.3, 123.3, 128.2,

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128.4, 131.8, 162.1, 167.8; IR (KBr, neat) 2981, 2939, 1709, 1626, 1134, 1043, 817, 745 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{17}O_3$ $(M + H)^+$ 245.1172, found 245.1172.

*(E)-Ethyl 3-((4-(2-Nitrophenyl)but-3-yn-1-yl)oxy)acrylate (**1d**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.54; yield 474 mg, 82%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 2.91 (t, J = 7.2 Hz, 2 H), 4.08 (t, J = 6.0 Hz, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.27 (d, J = 12.6 Hz, 1 H), 7.44 (t, J = 7.2 Hz, 1 H), 7.32 (d, J = 7.2 Hz, 1 H), 7.60 (d, J = 8.4 Hz, 1 H), 7.62 (d, J = 12.6 Hz, 1 H), 8.00 (d, J = 7.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 20.9, 60.1, 68.7, 78.0, 93.7, 97.6, 118.7, 124.7, 128.7, 132.9 (2C), 135.1, 162.0, 167.8; IR (KBr, neat) 2982, 2951, 1709, 1628, 1527, 1474, 1345, 1132, 1046, 476 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}NO_5$ $(M + H)^+$ 290.1023, found 290.1023.

*(E)-Ethyl 3-((4-(4-Chlorophenyl)but-3-yn-1-yl)oxy)acrylate (**1e**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.57; yield 445 mg, 80%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 2.81 (t, J = 6.6 Hz, 2 H), 4.03 (t, J = 6.6 Hz, 2 H), 4.17 (q, J = 7.2 Hz, 2 H), 5.26 (d, J = 12.6 Hz, 1 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.32 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 20.4, 60.0, 69.0, 81.6, 86.1, 97.3, 121.7, 128.7, 133.0, 134.2, 162.0, 167.8; IR (KBr, neat) 2981, 2937, 1709, 1626, 1489, 1135, 1092, 828 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{16}ClO_3$ $(M + H)^+$ 279.0782, found 279.0810.

*(E)-Methyl 2-(4-((3-Ethoxy-3-oxoprop-1-en-1-yl)oxy)but-1-yn-1-yl)benzoate (**1f**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.60; yield 526 mg, 87%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 2.85 (t, J = 6.8 Hz, 2 H), 3.86 (s, 3 H), 4.03 (t, J = 6.8 Hz, 2 H), 4.13 (q, J = 7.2 Hz, 2 H), 5.23 (d, J = 12.4 Hz, 1 H), 7.29 (t, J = 8.0 Hz, 1 H), 7.39 (t, J = 7.2 Hz, 1 H), 7.48 (d, J = 7.6 Hz, 1 H), 7.59 (d, J = 12.4 Hz, 1 H), 7.86 (d, J = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.7, 52.2, 59.9, 69.0, 81.2, 90.3, 97.2, 123.7, 127.8, 130.3, 131.7, 132.0, 134.4, 162.0, 166.6, 167.7; IR (KBr, neat) 2982, 2952, 1732, 1714, 1626, 1328, 1129, 1044, 960, 760 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}O_5$ $(M + H)^+$ 303.1227, found 303.1247.

*(E)-Ethyl 3-(Dec-3-yn-1-yloxy)acrylate (**1g**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.76; yield 506 mg, 91%; ^1H NMR (600 MHz, $CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3 H), 1.24−1.33 (m, 4 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.35−1.38 (m, 2 H), 1.44−1.49 (m, 2 H), 2.13−2.15 (m, 2 H), 2.54−2.58 (m, 2 H), 3.91 (t, J = 7.2 Hz, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.21 (d, J = 12.6 Hz, 1 H), 7.58 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 14.6, 18.9, 19.8, 22.8, 28.7, 29.0, 31.5, 60.0, 69.7, 75.1, 82.9, 97.1, 162.2, 167.9; IR (KBr, neat) 2932, 2857, 1713, 1628, 1134, 1046, 824 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{25}O_3$ $(M + H)^+$ 253.1798, found 253.1800.

*(E)-Ethyl 3-(Hex-3-yn-1-yloxy)acrylate (**1h**).* colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 313 mg, 80%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.10 (t, J = 7.2 Hz, 3 H), 1.26 (t, J = 7.2 Hz, 3 H), 2.14−2.16 (m, 2 H), 2.53−2.56 (m, 2 H), 3.91 (t, J = 7.2 Hz, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.21 (d, J = 12.6 Hz, 1 H), 7.58 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 12.6, 14.2, 14.3, 19.8, 61.5, 69.7, 81.7, 84.2, 97.2, 164.9, 167.9; IR (KBr, neat) 2978, 2850, 1716, 1625, 1242, 1181, 1025, 799 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{17}O_3$ $(M + H)^+$ 197.1172, found 197.1185.

*(E)-Ethyl 3-((4-(Thiophen-2-yl)but-3-yn-1-yl)oxy)acrylate (**1i**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.60; yield 405 mg, 81%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.83 (t, J = 6.8 Hz, 2 H), 4.00 (t, J = 7.2 Hz, 2 H), 4.16 (q, J = 7.2 Hz, 2 H), 5.25 (d, J = 12.4 Hz, 1 H), 6.93 (t, J = 4.8 Hz, 1 H), 7.15 (d, J = 4.0 Hz, 1 H), 7.20 (d, J = 4.8 Hz, 1 H), 7.61 (d, J = 12.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.4, 20.6, 60.0, 68.7, 75.8, 89.0, 97.3, 123.2, 126.8, 127.0, 131.9, 161.9, 167.7; IR (KBr, neat) 2981, 2905, 1710, 1625, 1328, 1132, 1045, 832, 703 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{15}O_3S$ $(M + H)^+$ 251.0736, found 251.0743.

*(E)-Ethyl 3-((6-Phenylhex-5-yn-3-yl)oxy)acrylate (**1j**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.56; yield 490 mg, 90%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.00 (t, J = 7.2 Hz, 3 H), 1.25 (t, J = 7.2 Hz, 3 H), 1.73−1.80 (m, 1 H), 1.82−1.87 (m, 1 H), 2.68 (dd, J = 17.4 and 6.6 Hz, 1 H), 2.73 (dd, J = 16.2 and 6.6 Hz, 1 H), 4.02−4.07 (m, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 5.32 (d, J = 12.6 Hz, 1 H), 7.27−7.29 (m, 3 H), 7.38−7.40 (m, 2 H), 7.62 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) 9.6, 14.6, 25.3, 27.1, 60.0, 83.3 (2 C), 85.1, 97.8, 123.4, 128.2, 128.4, 131.8, 162.5, 168.3; IR (KBr, neat) 2975, 2936, 1708, 1640, 1491, 1135, 1048, 758 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}O_3$ $(M + H)^+$ 273.1485, found 273.1485.

*(E)-Ethyl 3-((6-Phenylhex-1-en-5-yn-3-yl)oxy)acrylate (**1k**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 475 mg, 88%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.26 (t, J = 7.2 Hz, 3 H), 2.76 (dd, J = 16.8 and 6.6 Hz, 1 H), 2.85 (dd, J = 16.8 and 6.6 Hz, 1 H), 4.15 (q, J = 7.2 Hz, 2 H), 4.23 (q, J = 7.2 Hz, 1 H), 5.32−5.42 (m, 3 H), 5.88−5.95 (m, 1 H), 7.27−7.33 (m, 3 H), 7.38−7.41 (m, 2 H), 7.57 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (150 MHz,$CDCl_3$) δ 14.6, 26.5, 60.0, 81.8, 83.4, 84.6, 98.8, 119.2, 128.3, 128.5, 131.8, 132.0, 135.2, 161.3, 168.0; IR (KBr, neat) 2927, 2853,1707, 1644, 1475, 1134, 1044, 786 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{19}O_3$ $(M + H)^+$ 271.1329, found 271.1329.

*(E)-Ethyl 3-((1-Cyclopentyl-5-phenylpent-4-yn-2-yl)oxy)acrylate (**1l**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.60; yield 561 mg, 86%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23−1.31 (m, 4 H), 1.50−1.55 (m, 2 H), 1.63−1.70 (m, 2 H), 1.72−1.92 (m, 6 H), 2.64−2.77 (m, 2 H), 4.07−4.20 (m, 3 H), 5.32 (d, J = 12.0 Hz, 1 H), 7.27−7.30 (m, 3 H), 7.37−7.42 (m, 2 H), 7.63 (d, J = 12.0 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.6, 25.2, 25.3, 26.2, 32.7, 33.3, 36.6, 38.7, 40.5, 59.9, 83.1, 85.2, 97.8, 123.5, 128.2, 128.5, 131.8, 162.5, 168.2; IR (KBr, neat) 2953, 2863, 1709, 1642, 1371, 1131, 1045, 757 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{27}O_3$ $(M + H)^+$ 327.1955, found 327.1973.

*(E)-Ethyl 3-((1,4-Diphenylbut-3-yn-1-yl)oxy)acrylate (**1m**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.51; yield 512 mg, 80%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J = 7.6 Hz, 3 H), 2.91 (dd, J = 16.8 and 5.6 Hz, 1 H), 3.05 (dd, J = 16.8 and 7.2 Hz, 1 H), 4.08−4.14 (m, 2 H), 5.08 (t, J = 6.8 Hz, 1 H), 5.27 (d, J = 12.8 Hz, 1 H), 7.26−7.29 (m, 3 H), 7.34−7.40 (m, 7 H), 7.58 (d, J = 12.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 29.0, 60.0, 82.7, 83.5, 85.0, 99.1, 123.3, 126.4, 128.2, 138.4, 128.9, 129.0, 131.8, 138.9, 161.3, 167.8; IR (KBr, neat) 2953, 2924, 1709, 1640, 1491, 1128, 1040, 830 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{21}O_3$ $(M + H)^+$ 321.1485, found 321.1486.

*(E)-Ethyl 3-((1-(4-Chlorophenyl)-4-phenylbut-3-yn-1-yl)oxy)-acrylate (**1n**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.44; yield 552 mg, 78%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 2.89 (dd, J = 16.8 and 6.6 Hz, 1 H), 3.02 (dd, J = 16.8 and 5.4 Hz, 1 H), 4.07−4.14 (m, 2 H), 5.06 (t, J = 6.6 Hz, 1 H), 5.24 (d, J = 12.6 Hz, 1 H), 7.25−7.40 (m, 9 H), 7.56 (d, J = 12.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.9, 60.1, 81.8, 83.9, 84.4, 99.5, 123.2, 127.9, 128.4, 128.5, 129.2, 131.8, 134.8, 137.4, 160.9, 167.6; IR (KBr, neat) 2924, 2854, 1709, 1644, 1492, 1133, 1092, 758 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}ClO_3$ $(M + H)^+$ 355.1095, found 355.1095.

*(E)-Ethyl 3-((1-(4-Bromophenyl)-4-phenylbut-3-yn-1-yl)oxy)-acrylate (**1o**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.40; yield 666 mg, 84%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H), 2.88 (dd, J = 16.8 and 6.4 Hz, 1 H), 3.02 (dd, J = 16.8 and 6.4 Hz, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 5.05 (t, J = 6.4 Hz, 1 H), 5.25 (d, J = 12.4 Hz, 1 H), 7.24−7.31 (m, 5 H), 7.32−7.35 (m, 2 H), 7.52−7.56 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 28.8, 60.1, 81.8, 83.9, 84.3, 99.5, 122.9, 123.2, 128.2, 128.4, 128.5, 131.8 (2C), 132.1 (2C), 137.9, 160.9, 167.6; IR (KBr, neat) 2956, 2853, 1708, 1643, 1131, 1044, 822, 756 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{20}BrO_3$ $(M + H)^+$ 399.0590, found 399.0602.

*(E)-Ethyl 3-((4-Phenyl-1-(p-tolyl)but-3-yn-1-yl)oxy)acrylate (**1p**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 548 mg, 82%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.22 (t, J = 7.2 Hz, 3 H), 2.36 (s, 3 H), 2.88 (dd, J = 16.8 and 5.6 Hz, 1 H), 3.00 (dd, J = 16.8 and 7.6 Hz, 1 H), 4.05−4.15 (m, 2 H), 5.06 (t, J = 6.0 Hz, 1 H), 5.27 (d, J = 12.8 Hz, 1 H), 7.18−7.36 (m, 9 H), 7.58 (d, J = 12.8 Hz, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.5, 21.4, 28.9, 60.0, 82.7, 83.4, 85.1, 99.0, 126.4, 128.2, 128.4, 129.6 (2C), 131.8, 135.9, 138.7, 161.4, 167.9; IR (KBr, neat) 2924, 2954, 1709, 1641, 1491, 1132, 1044, 758 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{23}O_3$ $(M + H)^+$ 335.1642, found 335.1644.

General Procedure for the Synthesis of 2,3,5-Trisubstituted Tetrahydrofuran (2a−2p). To a suspension of $In(OTf)_3$ (0.5 mmol) in dry dichloromethane (1 mL) at 0 °C was added enol ether (1 mmol) in dry CH_2Cl_2 (2 mL) dropwise under nitrogen atmosphere. The reaction mixture was brought to room temperature. The reaction was continued for a specified time and monitored by TLC. After disappreance of the starting material, the reaction mixture was treated

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with saturated sodium bicarbonate solution (5 mL). The product was extracted with CH_2Cl_2 (2 × 10 mL), and the combined organic layer was washed with brine. The organic layer was separated and dried over anhydrous Na_2SO_4 and evaporated using a rotary evaporator to obtain the crude product. The crude product was purified by silica gel column chromatography using ethyl acetate and hexane as eluents to afford the cyclic compounds **2**.

*Ethyl 2-(3-(4-Methoxybenzoyl)tetrahydrofuran-2-yl)acetate (**2a**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.40; yield 176 mg, 60%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 2.13−2.18 (m, 1 H), 2.29−2.34 (m, 1 H), 2.60 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.64 (dd, J = 15.0 and 6.6 Hz, 1 H), 3.78−3.86 (m, 1 H), 3.87 (s, 3 H), 3.91 (q, J = 7.8 Hz, 1 H), 4.00−4.06 (m, 1 H), 4.09 (q, J = 7.2 Hz, 2 H), 4.59 (q, J = 6.6 Hz, 1 H), 6.95 (d, J = 8.4 Hz, 2 H), 7.96 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 32.0, 39.7, 50.4, 55.7, 60.8, 68.1, 78.1, 114.1, 129.8, 131.0, 164.0, 170.9, 198.4; IR (KBr, neat) 2962, 2876, 1732, 1670, 1600, 1259, 1171, 1027, 840 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}O_5$ (M + H)$^+$ 293.1384, found 293.1392.

*Ethyl 2-(3-(4-Methylbenzoyl)tetrahydrofuran-2-yl)acetate (**2b**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.30; yield 155 mg, 56%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 2.13−2.17 (m, 1 H), 2.32−2.36 (m, 1 H), 2.42 (s, 3 H), 2.61 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.66 (dd, J = 15.0 and 7.2 Hz, 1 H), 3.84−3.89 (m, 1 H), 3.91 (q, J = 7.8 Hz, 1 H), 4.00−4.05 (m, 1 H), 4.07 (q, J = 7.2 Hz, 2 H), 4.61 (q, J = 6.6 Hz, 1 H), 7.28 (d, J = 8.4 Hz, 2 H), 7.88 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.2, 21.8, 31.9, 39.7, 50.7, 60.8, 68.0, 77.9, 128.8, 129.6, 134.2, 144.5, 170.8, 199.4; IR (KBr, neat) 2978, 2873, 1734, 1677, 1607, 1449, 1177, 1059, 1033, 774 cm^{-1}; HRMS (ESI) calcd for $C_{16}H_{21}O_4$ (M + H)$^+$ 277.1434, found 277.1429.

*Ethyl 2-(3-Benzoyltetrahydrofuran-2-yl)acetate (**2c**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.30; yield 142 mg, 54%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.18 (t, J = 7.2 Hz, 3 H), 2.12−2.18 (m, 1 H), 2.32−2.39 (m, 1 H), 2.61 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, J = 15.0 and 7.8 Hz, 1 H), 3.86−3.93 (m, 2 H), 4.01−4.04 (m, 1 H), 4.06 (q, J = 7.2 Hz, 2 H), 4.62 (q, J = 6.6 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.97 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) 14.3, 32.0, 39.7, 50.8, 60.8, 68.0, 77.9, 128.7, 129.0, 133.6, 136.7, 170.8, 199.9; IR (KBr, neat) 2979, 2875, 1733, 1678, 1448, 1058, 1028, 698 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{19}O_4$ (M + H)$^+$ 263.1278, found 263.1273.

*Ethyl 2-(3-(4-Methoxybenzoyl)tetrahydrofuran-2-yl)acetate (**2a**) and Ethyl 2-(3-(4-Methoxyphenyl)-4-oxotetrahydro-2H-pyran-2-yl)-acetate (**3a**).* Colorless oil; R_f (hexane/EtOAc 4:1) 0.40; yield 122 mg, 42%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.12 (t, J = 7.2 Hz, 3 H, pyran), 1.17 (t, J = 7.2 Hz, 3 H, furan), 2.08−2.12 (m, 1 H, pyran), 2.18 (dd, J = 16.2 and 5.4 Hz, 1 H, furan), 2.29−2.34 (m, 1 H, furan), 2.42 (dd, J = 15.6 and 9.0 Hz, 1 H, pyran), 2.46−2.50 (m, 1 H, pyran), 2.60 (dd, J = 15.0 and 6.0 Hz, 1 H, furan), 2.64 (dd, J = 15.0 and 6.6 Hz, 1 H, furan), 3.78−3.86 (m, 1 H, furan), 3.87 (s, 3 H, pyran and furan), 3.91 (q, J = 7.8 Hz, 1 H, furan), 3.97 (m, 2 H, pyran), 4.00−4.06 (m, 1 H, furan), 4.05 (q, J = 7.2 Hz, 2 H, pyran), 4.09 (q, J = 7.2 Hz, 2 H, furan), 4.11−4.15 (m, 1 H, pyran), 4.17 (q, J = 7.8 Hz, 1 H, pyran), 4.59 (q, J = 6.6 Hz, 1 H, furan), 4.70−4.75 (m, 1 H, pyran), 6.95 (d, J = 8.4 Hz, 2 H, pyran and furan), 7.96 (d, J = 8.4 Hz, 2 H, pyran and furan).

*Ethyl 2-(3-(4-Chlorobenzoyl)tetrahydrofuran-2-yl)acetate (**2e**).* Colorless oil; R_f (hexane/EtOAc 8:1) 0.30; yield 133 mg, 45%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 2.12−2.16 (m, 1 H), 2.31−2.37 (m, 1 H), 2.61 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, J = 15.0 and 6.6 Hz, 1 H), 3.80−3.87 (m, 1 H), 3.91 (q, J = 7.2 Hz, 1 H), 4.01−4.05 (m, 1 H), 4.07 (q, J = 7.2 Hz, 2 H), 4.61 (q, J = 6.6 Hz, 1 H), 7.47 (d, J = 7.8 Hz, 2 H), 7.91 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 31.9, 39.6, 50.8, 60.9, 68.0, 77.9, 128.8, 129.3, 130.1, 135.0, 170.8, 198.8; IR (KBr, neat) 2980, 2876, 1732, 1681,1589, 1488, 1171, 1092, 1059, 834 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{18}ClO_4$ (M + H)$^+$ 297.0888, found 297.0898.

*Ethyl 2-(3-Heptanoyltetrahydrofuran-2-yl)acetate (**2g**).* Colorless oil; R_f (hexane/EtOAc 8:1) 0.30; yield 57 mg, 21%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.88 (t, J = 6.6 Hz, 3 H), 1.22−1.32 (m, 9 H), 1.58−1.60 (m, 2 H), 2.01−2.08 (m, 1 H), 2.14−2.21 (m, 1 H), 2.47 (t, J = 7.2 Hz, 2 H), 2.55 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.62 (dd, J = 15.0 and 7.2 Hz, 1 H), 2.97−3.01 (m, 1 H), 3.85 (q, J = 7.2 Hz, 1 H), 3.90−3.94 (m, 1 H), 4.12 (q, J = 7.2 Hz, 2 H), 4.42 (q, J = 6.0 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 14.4, 22.7, 23.7, 29.1, 29.2, 29.6, 30.4, 31.8, 40.1, 55.9, 60.9, 67.9, 170.9, 210.3; IR (KBr, neat) 2954, 2856, 1732, 1711, 1629, 1172, 1062, 1032, 726 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{27}O_4$ (M + H)$^+$ 271.1904, found 271.1899.

*Ethyl 2-(3-Propionyltetrahydrofuran-2-yl)acetate (**2h**).* Colorless oil; R_f (hexane/EtOAc 8:1) 0.28; yield 57 mg, 30%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, J = 6.8 Hz, 3 H), 1.25 (t, J = 6.8 Hz, 3 H), 2.02−2.30 (m, 1 H), 2.16−2.23 (m, 1 H), 2.51−2.58 (m, 3 H), 2.63 (dd, J = 15.2 and 6.8 Hz, 1 H), 2.97−3.03 (m, 1 H), 3.85 (dd, J = 15.2 and 8.4 Hz, 1 H), 3.92 (dd, J = 14.4 and 8.4 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 4.43 (q, J = 6.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.8, 14.4, 30.5, 35.9, 40.1, 55.7, 60.9, 67.9, 77.6, 171.0, 210.7; IR (KBr, neat) 2980, 2849, 1739, 1693, 1172, 1094, 1030, 802 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_{19}O_4$ (M + H)$^+$ 215.1278, found 215.1272.

*Ethyl 2-(3-(Thiophene-2-carbonyl)tetrahydrofuran-2-yl)acetate (**2i**).* Colorless oil; R_f (hexane/EtOAc 3:1) 0.40; yield 180 mg, 67%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 2.24−2.37 (m, 2 H), 2.61−2.72 (m, 2 H), 3.75 (q, J = 6.8 Hz, 1 H), 3.96 (q, J = 7.2 Hz, 1 H), 4.00−4.10 (m, 3 H), 4.56 (q, J = 6.4 Hz, 1 H), 7.17 (t, J = 4.8 Hz, 1 H), 7.69 (t, J = 4.8 Hz, 1 H), 7.79 (d, J = 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ14.3, 32.1, 39.7, 52.2, 60.9, 68.2, 78.3, 128.5, 132.6, 134.7, 144.4, 170.7, 192.8; IR (KBr, neat) 2925, 2855, 1732, 1659, 1415, 1160, 1094, 729 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{17}O_4S$ (M + H)$^+$ 269.0842, found 269.0842.

*Ethyl 2-(3-Benzoyl-5-ethyltetrahydrofuran-2-yl)acetate (**2j**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.40; yield 244 mg, 84%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.93 (t, J = 7.2 Hz, 3 H), 1.13 (t, J = 7.2 Hz, 3 H), 1.49−1.54 (m, 1 H), 1.65−1.70 (m, 1 H), 1.94−1.99 (m, 1 H), 2.14−2.19 (m, 1 H), 2.61 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.68 (dd, J = 15.0 and 6.0 Hz, 1 H), 3.89−3.96 (m, 2 H), 4.04 (q, J = 7.2 Hz, 2 H), 4.62 (q, J = 6.0 Hz, 1 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.58 (d, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.3, 14.3, 28.5, 36.9, 40.1, 50.7, 60.8, 77.5, 80.6, 128.6, 128.9, 133.5, 136.8, 170.9, 200.3; IR (KBr, neat) 2967, 2876, 1735, 1680, 1597, 1450, 1173, 1096, 1051, 700 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{23}O_4$ (M + H)$^+$ 291.1591, found 291.1568.

*Ethyl 2-((2S,3R)-3-Benzoyl-5-vinyltetrahydrofuran-2-yl)acetate (**2k**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.37; yield 181 mg, 63%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 2.09−2.14 (m, 1 H), 2.27−2.32 (m, 1 H), 2.64 (dd, J = 15.0 and 6.6 Hz, 1 H), 2.72 (dd, J = 15.0 and 6.0 Hz, 1 H), 3.95−3.82 (m, 1 H), 4.05 (q, J = 7.2 Hz, 2 H), 4.50 (q, J = 6.6 Hz, 1 H), 4.68 (q, J = 6.6 Hz, 1 H), 5.15 (d, J = 10.8 Hz, 1 H), 5.29 (d, J = 16.2 Hz, 1 H), 5.83−5.90 (m, 1 H), 7.47−7.50 (m, 2 H), 7.58 (t, J = 7.8 Hz, 1 H), 7.95 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 37.7, 40.1, 50.8, 60.8, 77.9, 80.1, 116.6, 128.7, 129.0, 133.6, 136.7, 138.2, 170.8, 200.0; IR (KBr, neat) 2923, 2853, 1733, 1679, 1594, 1448, 1173, 1033, 1006, 692 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{21}O_4$ (M + H)$^+$ 289.1434, found 289.1429.

*Ethyl 2-((2S,3R,5S)-3-Benzoyl-5-(cyclopentylmethyl)tetrahydrofuran-2-yl)acetate (**2l**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.50; yield 217 mg, 63%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.15 (t, J = 7.2 Hz, 3 H), 1.45−1.50 (m, 4 H), 1.57−1.62 (m, 3 H), 1.69−1.85 (m, 4 H), 1.92−1.98 (m, 1 H), 2.15−2.19 (m, 1 H), 2.60 (dd, J = 15.0 and 6.6 Hz, 1 H), 2.68 (dd, J = 15.0 and 6.0 Hz, 1 H), 3.89−3.93 (m, 1 H), 4.00−4.07 (m, 3 H), 4.60 (q, J = 6.0 Hz, 1 H), 7.47 (t, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.2 Hz, 1 H), 7.95 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 25.1, 25.2, 33.1, 37.5, 37.9, 40.2, 42.1, 50.7, 60.7, 71.1, 77.5, 78.9, 128.7, 128.9, 133.5, 136.8, 170.9, 200.4; IR (KBr, neat) 2949, 2866, 1738, 1676, 1449, 1162, 1052, 709 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{29}O_4$ (M + H)$^+$ 345.2060, found 345.2076.

*Ethyl 2-(3-Benzoyl-5-phenyltetrahydrofuran-2-yl)acetate (**2m**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.37; yield 311 mg, 92%; ^{1}H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 2.25−2.31 (m, 1 H), 2.51−2.55 (m, 1 H), 2.76 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.83 (dd, J = 15.0 and 5.4 Hz, 1 H), 4.06−4.11 (m, 3 H), 4.82 (q, J = 6.6 Hz, 1 H), 5.10 (dd, J = 7.8 and 7.8 Hz, 1 H), 7.26−7.28 (m, 1 H), 7.33−7.37 (m, 4 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.56−7.60 (m, 1 H), 7.97 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 29.9, 39.9, 50.7, 60.9, 78.0, 80.7, 126.0, 127.9, 128.6, 128.7, 129.0, 133.7, 136.6, 141.8, 170.8, 200.1; IR

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(KBr, neat) 2921, 2852, 1731, 1679, 1614, 1448, 1130, 1060, 1031, 700 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{23}O_4$ $(M + H)^+$ 339.1591, found 339.1593.

*Ethyl 2-((2S,3R,5R)-3-Benzoyl-5-(4-chlorophenyl)tetrahydrofuran-2-yl)acetate (**2n**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.32; yield 264 mg, 71%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 2.15−2.26 (m, 1 H), 2.49−2.55 (m, 1 H), 2.75 (dd, J = 15.2 and 6.0 Hz, 1 H), 2.81 (dd, J = 15.2 and 6.0 Hz, 1 H), 4.02−4.12 (m, 3 H), 4.81 (q, J = 6.0 Hz, 1 H), 5.03 (dd, J = 8.4 and 6.8 Hz, 1 H), 7.27−7.33 (m, 4 H), 7.47−7.51 (m, 2 H), 7.56−7.62 (m, 1 H), 7.97 (d, J = 7.6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 39.8 40.1, 50.5, 60.9, 78.1, 80.0, 127.4, 128.7, 128.8, 129.0, 133.5, 133.7, 136.5, 140.4, 170.7, 199.9; IR (KBr, neat) 2977, 2929, 1734, 1678, 1492, 1447, 1168, 1011, 823, 696 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}ClO_4$ $(M + H)^+$ 373.1201, found 373.1178.

*Ethyl 2-((2S,3R,5R)-3-Benzoyl-5-(4-bromophenyl)tetrahydrofuran-2-yl)acetate (**2o**).* Colorless solid; mp 79−81 °C; R_f (hexane/EtOAc 9:1) 0.30; yield 300 mg, 72%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 2.16−2.23 (m, 1 H), 2.50−2.54 (m, 1 H), 2.75 (dd, J = 15.0 and 6.6 Hz, 1 H), 2.80 (dd, J = 15.0 and 6.0 Hz, 1 H), 4.06−4.10 (m, 3 H), 4.80 (q, J = 6.6 Hz, 1 H), 5.02 (dd, J = 7.8 and 7.8 Hz, 1 H), 7.24 (q, J = 8.4 Hz, 2 H), 7.45−7.50 (m, 4 H), 7.59 (t, J = 7.2 Hz, 1 H), 7.96 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 39.6, 39.9, 50.3, 60.7, 77.9, 79.8, 121.4, 127.5, 128.5, 128.8, 131.5, 133.6, 136.3, 140.7, 170.5, 199.7; IR (KBr, neat) 2925, 2856, 1732, 1679, 1488, 1012, 816, 695 cm^{-1}; HRMS (ESI) calcd for $C_{21}H_{22}BrO_4$ $(M + H)^+$ 417.0696, found 417.0695 and 419.0682.

*Ethyl 2-(3-Benzoyl-5-(p-tolyl)tetrahydrofuran-2-yl)acetate (**2p**).* Colorless oil; R_f (hexane/EtOAc 9:1) 0.36; yield 285 mg, 81%; ^1H NMR (600 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3 H), 2.24−2.30 (m, 1 H), 2.34 (s, 3 H), 2.47−2.52 (m, 1 H), 2.75 (dd, J = 15.0 and 6.0 Hz, 1 H), 2.82 (dd, J = 15.0 and 6.0 Hz, 1 H), 4.05−4.10 (m, 3 H), 4.80 (q, J = 6.0 Hz, 1 H), 5.03 (dd, J = 7.8 and 7.2 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 2 H), 7.25 (d, J = 7.8 Hz, 2 H), 7.48 (t, J = 7.8 Hz, 2 H), 7.56−7.60 (m, 1 H), 7.96 (d, J = 7.8 Hz, 2 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 14.3, 21.4, 29.9, 40.0, 50.8, 60.9, 78.0, 80.6, 126.0, 128.7, 129.0, 129.3, 133.6, 136.7, 138.8, 170.8, 200.1; IR (KBr, neat) 2925, 2854, 1733, 1680, 1616, 1450, 1131, 1057, 1031, 813, 701 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{25}O_4$ $(M + H)^+$ 353.1747, found 353.1748.

General Procedure for the Beckmann Rearrangement. A solution of tetrahydrofuran (1.1 mmol), hydroxylamine hydrochloride (1.1 mmol), and sodium acetate (1.1 mmol) in methanol (3 mL) was refluxed, and the reaction was monitored by TLC. After completion of the reaction, methanol was evaporated under vacuo and diluted with water, and the product was extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under vacuo. The crude E/Z oxime was dissolved in diethyl ether (1 mL) and treated with $SOCl_2$ (1.1 mmol), and the reaction was continued overnight. The solvent and residual $SOCl_2$ were removed under vacuo, and the product was purified by silica gel column chromatography using hexane:EtOAc as eluents.

*Ethyl 2-(3-(Phenylcarbamoyl)tetrahydrofuran-2-yl)acetate (**4c**) and Ethyl 2-(3-Benzamidotetrahydrofuran-2-yl)acetate (**5c**) (**4c:5c**::9:1).* Semisolid, R_f (hexane/EtOAc, 4:1) 0.35; yield 69 mg, 50%; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (t, J = 7.2 Hz, 3 H, **4c** and **5c**), 1.99−2.08 (m, 1 H, **4c** and **5c**), 2.47−2.56 (m, 1 H, **4c** and **5c**), 2.63 (dd, J = 16.0 and 8.4 Hz, 1 H, **4c**), 2.70 (dd, J = 16.4 and 8.4 Hz, 1 H, **5c**), 2.76−2.84 (m, 1 H, **4c** and **5c**), 2.90−2.96 (m, 1 H, **4c** and **5c**), 3.88 (q, J = 7.6 Hz, 1 H, **4c** and **5c**), 3.92−3.90 (m, 1 H, **4c** and **5c**), 4.12 (q, J = 7.6 Hz, 2 H, **5c**), 4.19 (q, J = 7.2 Hz, 2 H, **4c**), 4.33 (t, J = 6.4 Hz, 1 H, **5c**), 4.38−4.46 (m, 1 H, **4c**), 7.09 (t, J = 7.2 Hz, 1 H, **4c** and **5c**), 7.29−7.34 (m, J = 7.2 Hz, 2 H, **4c**), 7.37−7.44 (m, 2 H, **5c**), 7.57 (d, J = 7.2 Hz, 2 H, **4c** and **5c**), 8.56 (brs, 1 H, **5c**), 8.70 (brs, 1 H, **4c**); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 20.1, 29.1, 39.7, 40.0, 51.1, 61.4, 63.1, 68.5, 78.6, 78.7, 119.8, 124.2, 124.3, 128.3, 128.5, 129.1, 131.8, 138.5, 170.9, 172.6; IR (KBr, neat) 3319, 2980, 2885, 1731, 1666, 1600, 1539, 1443, 1311, 1163, 1067, 1028, 757 cm^{-1}; HRMS (ESI) calcd for $C_{15}H_{20}NO_4$ $(M + H)^+$ 278.1387, found 278.1396.

*Ethyl 2-(5-Ethyl-3-(phenylcarbamoyl)tetrahydrofuran-2-yl)-acetate (**4j**).* Semisolid, R_f (hexane/EtOAc, 4:1) 0.38; yield 64 mg, 42%; ^1H NMR (600 MHz, $CDCl_3$) δ 0.96 (t, J = 7.2 Hz, 3 H), 1.13 (t, J = 7.2 Hz, 3 H), 1.58−1.68 (m, 1 H), 1.74−1.84 (m, 1 H), 2.02−2.10 (m, 1 H), 2.22−2.30 (m, 1 H), 2.66 (dd, J = 16.4 and 8.8 Hz, 1 H), 2.81 (dd, J = 16.4 and 5.6 Hz, 1 H), 3.18 (q, J = 7.6 Hz, 1 H), 3.74−3.82 (m, 1 H), 3.98−4.10 (m, 2 H), 4.34 (q, J = 7.2 Hz, 1 H), 7.07 (t, J = 7.6 Hz, 1 H), 7.28 (t, J = 8.0 Hz, 2 H), 7.47 (d, J = 8.0 Hz, 2 H), 7.60 (brs, 1 H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 10.6, 14.2, 28.3, 30.0, 34.9, 36.7, 49.7, 61.1, 80.8, 119.8, 124.5, 129.2, 138.1, 170.9, 172.5; IR (KBr, neat) 3444, 2925, 2856, 1731, 1666, 1600, 1540, 1443, 1311, 1177, 1034, 755 cm^{-1}; HRMS (ESI) calcd for $C_{17}H_{24}NO_4$ $(M + H)^+$ 306.1700, found 306.1709.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C NMR spectra of all new compounds, crystal parameters, and ORTEP diagram of compound **2o** are included. This material 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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