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An Unexpected 2,3-Dihydrofuran Derivative Ring Opening Initiated by Electrophilic Bromination: Scope and Mechanistic Study

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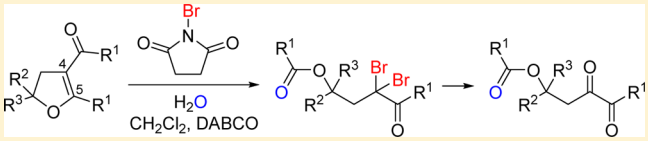
Supporting Information

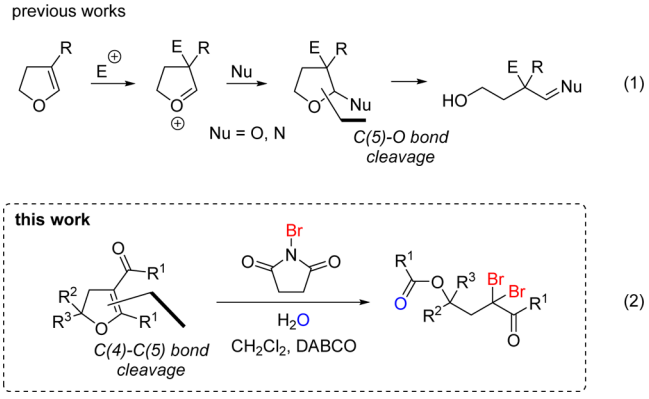
ABSTRACT: An unexpected 2,3-dihydrofuran ring opening process at the C(4)−C(5) bond has been developed. *N*-Bromosuccinimide and DABCO were used as the electrophilic halogen source and the catalyst, respectively. Mechanistic study indicates that moisture in the solvent might contribute to the reaction. The resulting brominated product could be further oxidized to yield a synthetically valuable 1,2-diketo building block.



INTRODUCTION

Furan and its derivatives are important heterocyclic subunits which distribute widely in various biologically active natural products and pharmaceutically important compounds.[1] Among them, 2,3-dihydrofuran derivatives, which possess a reactive enol ether moiety, serve not only as an essential motif that forms the basic structure of many natural products, e.g., aflatoxins,[2] but also as an important synthetic intermediate that could be further manipulated in various reactions such as aromatization to furans or ring opening to linear chain compounds.[1b,3] Most of the 2,3-dihydrofuran ring opening reactions may proceed through the cleavage of the C(5)−oxygen bond. Typically, the enol ether moiety reacts with electrophiles to give the oxonium cationic intermediates followed by the attack of various nucleophiles to give the corresponding adducts, which can undergo ring opening to yield the alcohol derivatives (Scheme 1, eq 1). For example, water can be used as the nucleophile to give the lactol product, and this strategy has been applied in the synthesis of 4-ketoundecanoic acid.[4,5] In contrast, to the best of our knowledge there is no report on the cleavage of the C(4)−C(5) bond which led to the 2,3-dihydrofuran ring opening. Herein, we are pleased to report a novel ring opening reaction of 2,3-dihydrofuran derivatives to efficiently yield various linear chain keto-carboxylate products (Scheme 1, eq 2).

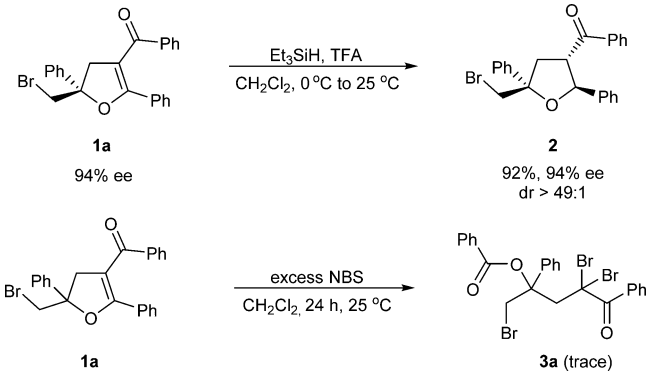
Scheme 1. An Unexpected C(4)−C(5) Bond Cleavage of 2,3-Dihydrofuran



RESULTS AND DISCUSSION

Recently, we developed a facile and highly enantioselective bromocyclization of olefinic 1,3-dicarbonyl compounds using amino-thiocarbamate as the catalyst.[6] The resulting 2,3-dihydrofurans **1** are valuable building blocks. We found that **1a** could readily undergo a classical acid-mediated conjugated addition process to yield highly functionalized THF system **2**.[7] Surprisingly, treatment of **1a** with an excess amount of *N*-bromosuccinimide (NBS) or bromine in CH_2Cl_2 at 25 °C for 72 h gave a trace amount of unknown compound. After extensive physical analysis, the unknown product was identified to be tribromide **3a**, which is the result of the C(4)−C(5) bond cleavage in the 2,3-dihydrofuran system (Scheme 2). The reaction rate was enhanced significantly when 20 mol % of 1,4-

Scheme 2. Reactions Using 1a as the Substrate



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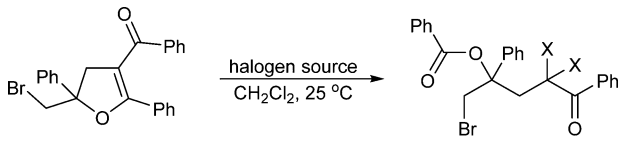
diazabicyclo[2.2.2]octane (DABCO) was added, and the transformation was readily scalable (Table 1, entries 2 and 3). Other catalysts including $SPPh_3$, PPh_3, and DBU were also examined, but poor catalytic abilities were observed (entries 4–6). The reaction remained sluggish even when more electrophilic halogen source bromine was used. On the other hand, a good yield of **3a** was obtained when bromine together with a catalytic amount of DABCO was used (entries 7 and 8). No reaction was observed when *N*-iodosuccinimide (NIS) was used, while dichloride **3a** (X = Cl) was obtained in excellent yield when *N*-chlorosuccinimide (NCS) was used as the halogen source (entries 9 and 10).[8] The structure of **3a** (X = Cl) was also confirmed by an X-ray crystallographic study.

Table 1. Reaction Optimization[a]



1a **3a**

entry	halogen source	catalyst	X	time (h)	yield (%)[b]
1	NBS	none	Br	72	trace
2	NBS	DABCO	Br	3	95
3[c]	NBS	DABCO	Br	3	90
4	NBS	PPh_3	Br	72	32
5	NBS	$SPPh_3$	Br	72	trace
6	NBS	DBU	Br	72	trace
7	Br_2	none	Br	72	0
8	Br_2	DABCO	Br	3	92
9	NCS	DABCO	Cl	3	88
10	NIS	DABCO	I	3	trace

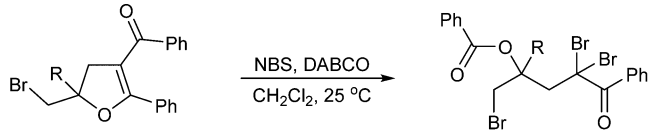
[a]Reactions were carried out with **1a** (0.02 mmol), halogen source (0.05 mmol), and catalyst (0.004 mmol) in CH_2Cl_2 (AR grade, 1 mL). [b]Isolated yield. [c]Reaction was conducted using 1.0 mmol of **1a**.

Other substrates were then subjected to investigation. 2,3-Dihydrofuran **1** with different R substitutents were first studied, and the results are shown in Table 2. It was found that both electron-deficient (**1b**–**1g**) and electron-rich (**1h**–**1i**) substituted substrates worked well under the optimized conditions. In addition, **1j** with a 3-thienyl substituent worked well to give **3j** in 83% yield, and no bromination at the thiophene was observed. Substrates with a 2-naphthyl or a methyl substitution could also give the desired products **3k** or **3l**, respectively, in good isolated yield.

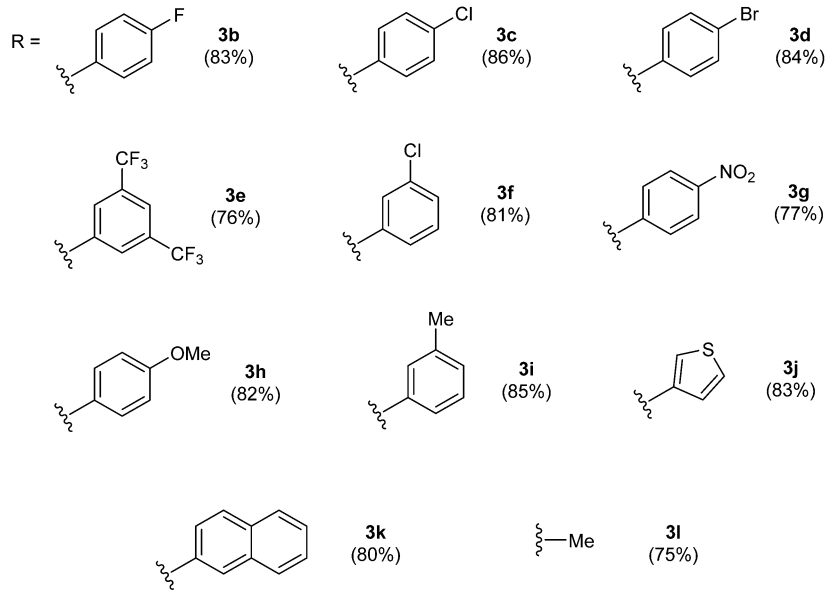
We also examined the substrate **4** with different R subsituents at the α-oxygen positions. To our delight, good chemical yields were obtained regardless of the nature of substitution including the electron-deficient *p*-chlorophenyl and the electron-rich *p*-methoxyphenyl and *tert*-butyl groups (Table 3).

To get better insight on this type of ring opening process, a number of experiments were performed. In the presence of 4 Å molecular sieves, no reaction was observed and the starting material was recovered quantitatively (Scheme 3, eq 1), suggesting that moisture (potentially from solvent) might contribute to the reaction. On the other hand, methyl ether adduct **6** was obtained in 76% yield when MeOH was used as

Table 2. NBS Mediated Ring Opening of 1[a]



1 **3**



[a]Reactions were carried out with **1** (0.02 mmol), NBS (0.05 mmol), and DABCO (0.004 mmol) in CH_2Cl_2 (AR grade, 1 mL). The yields were isolated yields.

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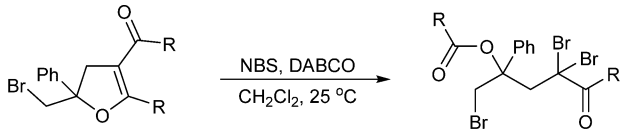
Table 3. NBS Mediated Ring Opening of 4[a]

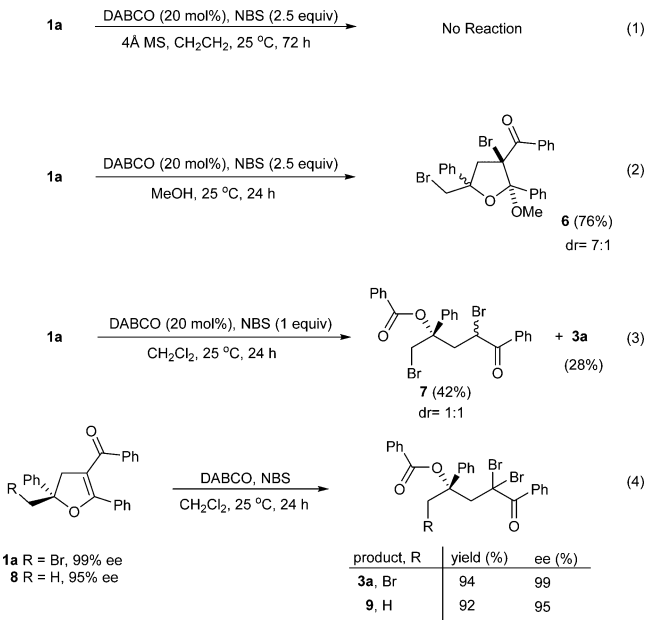


4 5

entry	R	product	yield (%)
1	4-Cl-C_6H_4	**5a**	78
2	4-MeO-C_6H_4	**5b**	82
3	*t*-Bu	**5c**	85

[a]Reactions were carried out with **4** (0.02 mmol), NBS (0.05 mmol), and DABCO (0.004 mmol) in CH_2Cl_2 (AR grade, 1 mL). The yields were isolated yields.

Scheme 3. Mechanistic Studies



the solvent. (Scheme 3, eq 2). When only 1 equiv of NBS was used, a significant amount of ring opening product **7** (42%) was obtained together with 28% of the dibromide product **3a**, and 25% of the starting material was recovered (Scheme 3, eq 3). Enantioenriched substrate **1a** (99% ee) was also examined, and the corresponding product **3a** was obtained in 94% yield without ee erosion. The debrominated substrate **8** (95% ee) also returned the ring opening product **9** in good yield without loss of optical purity (Scheme 3, eq 4). This suggests that the Br unit in 2,3-dihydrofuran **1** might not be involved in the ring opening process.[7,9]

Since DABCO showed superior catalytic ability over other Lewis base catalysts (Table 1), we suspect that DABCO might activate the enone moiety in the 2,3-dihydrofuran through a Morita−Baylis−Hillman type mechanism to give intermediate **A** (Scheme 4).[10] Subsequent trapping of the enolate by the electrophilic Br could give **B**. Regeneration of DABCO followed by nucleophilic attack of the oxonium intermediate by a water molecule could give hemiacetal **C**. This result is also in alignment with the observation that, in the presence of a better nucleophile, MeOH, the methyl ether adduct **6** was obtained (Scheme 3, eq 2). Ring opening through C(4)−C(5) bond cleavage could yield intermediate **D1**. Although classically the 2,3-dihydrofuran hemiacetal ring opening takes place at the C(5)−O bond,[4,5] we speculate that the presence of an electron-withdrawing Br group at the α-keto position might further stabilize the anion (i.e., the resonance intermediate **D2**) which might override the inherent ring opening preference. In the presence of only 1 equiv of NBS, intermediate **D** might be quenched by proton instead of the electrophilic Br to yield product **7** (Scheme 3, eq 3). Finally, electrophilic bromination of **D** could furnish the ring opening product.

The keto-benzoate product **3a** could be further manipulated to give interesting diketo benzoate compound **10**, which is a useful building block of flavoring substances,[11] in 76% yield using the SmI_2−H_2O protocol developed by Procter (Scheme 5).[12]

In summary, a novel and efficient ring opening reaction of 2,3-dihydrofuran derivatives was developed. NBS and DABCO were used as the electrophilic halogen source and the catalyst, respectively. The resulting α,α-dibromoketone compound can be further oxidized to give a useful 1,2-diketo building block.

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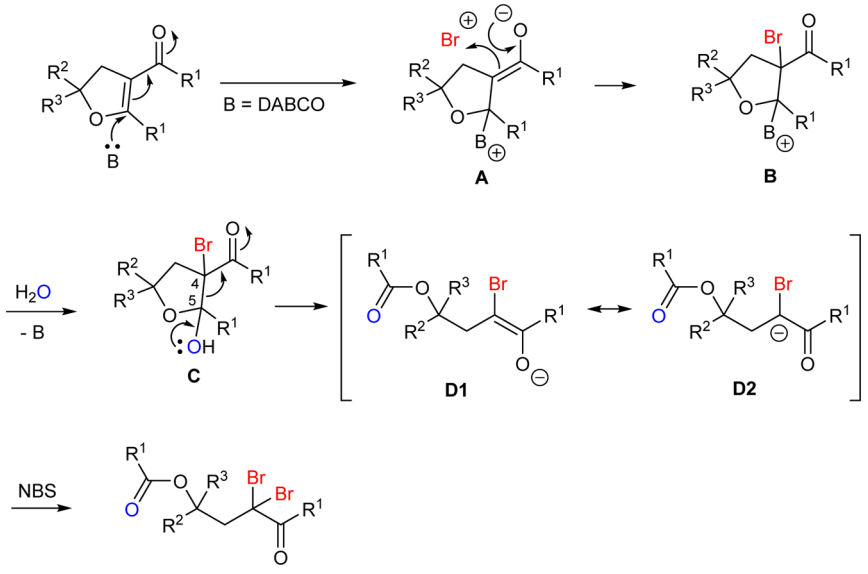
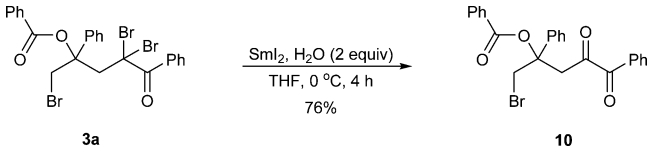
Scheme 4. A Plausible Mechanism



Scheme 5. Oxidation of 3a



EXPERIMENTAL SECTION

A. Materials and Methods. All reactions that required anhydrous conditions were carried by standard procedures under nitrogen atmosphere. Commercially available reagents and solvents were used without further treatment. Tetrahydrofuran (THF) was freshly distilled prior to use from sodium/benzophenone ketyl under N_2. CH_2Cl_2 was freshly distilled from CaH_2. Thin-layer chromatography (TLC) was performed using precoated silica gel foils, and compounds were visualized with a spray of 5% (w/v) dodecamolybdophosphoric acid in ethanol and subsequent heating. Chromotographic purification was performed on silica gel (0.040−0.063 mm). ^1H and ^{13}C NMR spectra were recorded on a spectrometer operating at 300 MHz for proton and 75 MHz for carbon nuclei or 500 MHz for proton and 125 MHz for carbon nuclei. Data for ^1H NMR spectra are reported as follows: chemical shift δ ppm (multiplicity, coupling constant (Hz), integration). Data for ^1H NMR spectra are referenced to the center line of $CDCl_3$ (δ 7.26) as the internal standard. Data for ^{13}C NMR spectra are referenced to the center line of $CDCl_3$ (δ 77.0). High resolution mass spectra were obtained on a spectrometer in ESI or EI mode using a TOF mass analyzer.

B. General Procedure for the Ring Opening Reaction. To a solution of 2,3-dihydrofuran derivatives[6] (0.02 mmol, 1 equiv) and DABCO (0.67 mg, 0.004 mmol, 0.2 equiv) in dichloromethane (AR grade, 1 mL) at 25 °C in the absence of light was added *N*-bromosuccinimide (13.4 mg, 0.05 mmol, 2.5 equiv). The resulting mixture was stirred at the same temperature for 3 h. The reaction was quenched with saturated Na_2SO_3 (3 mL), and the solution was diluted with water (3 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined extracts were washed with brine (5 mL), dried with $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by flash column chromatography (EtOAc:hexanes = 1:9) to yield the corresponding product.

*1,4,4-Tribromo-5-oxo-2,5-diphenylpentan-2-yl Benzoate (**3a**, X = Br).* Yellow oil (11.2 mg, 95% yield); $[\alpha]_D^{25}$ +179 (*c* 1.0, $CHCl_3$, 99% ee); IR (KBr) 2880, 1758, 1664, 1240, 982, 779 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20−8.06 (m, 2H), 7.86 (d, *J* = 7.5 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.53−7.39 (m, 5H), 7.39−7.29 (m, 5H), 4.71 (d, *J* = 11.0 Hz, 1H), 4.45 (d, *J* = 11.0 Hz, 1H), 4.36 (d, *J* = 15.7 Hz, 1H), 3.98 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 165.1, 138.1, 133.2, 132.7, 132.6, 130.7, 130.5, 129.9, 128.4, 128.4, 128.2, 127.6, 126.5, 84.4, 59.3, 50.9, 39.2; HRMS (ESI) calcd for $C_{24}H_{19}Br_3O_3Na$ *m*/*z* $[M + Na]^+$ 614.8782, found 614.8777; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm) t_1 = 8.7 min (minor), t_2 = 9.2 min (major).

*1-Bromo-4,4-dichloro-5-oxo-2,5-diphenylpentan-2-yl Benzoate (**3a**, X = Cl).* White foam (10.4 mg, 88% yield); $[\alpha]_D^{25}$ +223 (*c* 1.0, $CHCl_3$, 99% ee); IR (KBr) 3080, 2451, 2273, 1789, 1687, 1381, 1133, 971, 793 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 7.3 Hz, 2H), 8.00−7.78 (m, 2H), 7.59 (d, *J* = 7.3 Hz, 1H), 7.56−7.41 (m, 5H), 7.41−7.29 (m, 5H), 4.74 (d, *J* = 11.0 Hz, 1H), 4.46 (d, *J* = 10.9 Hz, 1H), 4.09 (d, *J* = 15.7 Hz, 1H), 3.69 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.0, 165.1, 138.6, 133.2, 133.1, 131.8, 130.6, 130.5, 129.8, 128.4, 128.4, 128.1, 127.8, 126.2, 83.7, 83.4, 49.0, 39.2; HRMS (ESI) calcd for $C_{24}H_{19}BrCl_2O_3Na$ *m*/*z* $[M + Na]^+$ 526.9792, found 526.9781; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm) t_1 = 8.7 min (minor), t_2 = 9.2 min (major).

*1,4,4-Tribromo-2-(4-fluorophenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3b**).* Yellow oil (10.1 mg, 83% yield); $[\alpha]_D^{25}$ +165 (*c* 1.0, $CHCl_3$, 90% ee); IR (KBr) 3059, 2781, 2665, 1701, 1686, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.2, 1.1 Hz, 2H), 7.90 (dd, *J* = 8.5, 1.1 Hz, 2H), 7.65−7.56 (m, 1H), 7.54−7.44 (m, 3H), 7.44−7.39 (m, 2H), 7.36 (t, *J* = 7.9 Hz, 2H), 7.07−6.97 (m, 2H), 4.72 (d, *J* = 11.1 Hz, 1H), 4.39 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.95 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 165.1, 163.4, 161.4, 133.9, 133.3, 133.0, 132.3, 130.6, 129.9, 128.5, 128.4, 127.7, 115.4, 115.2, 84.1, 59.2, 50.8, 38.9; HRMS (ESI) calcd for $C_{24}H_{18}Br_3FO_3Na$ *m*/*z* $[M + Na]^+$ 632.8688, found 632.8671; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 230 nm) t_1 = 11.5 min (minor), t_2 = 12.7 min (major).

*1,4,4-Tribromo-2-(4-chlorophenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3c**).* Yellow oil (10.8 mg, 86% yield); $[\alpha]_D^{25}$ +139 (*c* 1.0, $CHCl_3$, 87% ee); IR (KBr) 3089, 2856, 1768, 1654, 1523, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18−8.02 (m, 2H), 7.95−7.79 (m, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.53−7.44 (m, 3H), 7.36 (dd, *J* = 12.3, 5.3 Hz, 4H), 7.33−7.27 (m, 2H), 4.71 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.34 (d, *J* = 15.8 Hz, 1H), 3.95 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 165.1, 136.6, 134.3, 133.4, 133.0, 132.3, 130.5, 130.5, 129.9, 128.5, 128.5, 128.0, 127.7, 84.0, 59.1, 50.8, 38.7; HRMS (ESI) calcd for $C_{24}H_{18}Br_3ClO_3Na$ *m*/*z* $[M + Na]^+$ 648.8392, found 648.8376; HPLC (Daicel Chiralpak IC, *i*-PrOH/

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hexane = 10/90, 0.6 mL/min, 230 nm) t_1 = 11.5 min (minor), t_2 = 13.5 min (major).

*1,4,4-Tribromo-2-(4-bromophenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3d**).* Yellow oil (11.3 mg, 84% yield); $[\alpha]_D^{25}$ +265 (*c* 1.0, $CHCl_3$, 90% ee); IR (KBr) 3077, 1765, 1694, 1102, 1007, 984 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (d, *J* = 7.5 Hz, 2H), 7.87 (d, *J* = 7.7 Hz, 2H), 7.60 (t, *J* = 7.4 Hz, 1H), 7.48 (ddd, *J* = 12.7, 12.0, 6.4 Hz, 5H), 7.36 (t, *J* = 7.8 Hz, 2H), 7.31 (d, *J* = 8.6 Hz, 2H), 4.71 (d, *J* = 11.1 Hz, 1H), 4.38 (d, *J* = 11.1 Hz, 1H), 4.35 (d, *J* = 15.8 Hz, 1H), 3.95 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 165.0, 137.1, 133.4, 133.0, 132.3, 131.5, 130.5, 130.4, 129.9, 128.5, 128.3, 127.7, 122.5, 84.0, 59.1, 50.8, 38.5; HRMS (ESI) calcd for $C_{24}H_{18}Br_4O_3Na$ *m*/*z* $[M + Na]^+$ 692.7887, found 692.7869; HPLC (Daicel Chiralpak IC, *i*-PrOH/hexane = 10/90, 0.6 mL/min, 230 nm) t_1 = 11.8 min (minor), t_2 = 14.5 min (major).

*2-(3,5-Bis(trifluoromethyl)phenyl)-1,4,4-tribromo-5-oxo-5-phenylpentan-2-yl Benzoate (**3e**).* Yellow oil (11.1 mg, 76% yield); IR (KBr) 3068, 1725, 1628, 1371, 967, 757 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11−8.04 (m, 2H), 7.97 (s, 2H), 7.93−7.85 (m, 3H), 7.67−7.59 (m, 1H), 7.54−7.45 (m, 3H), 7.39−7.31 (m, 2H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.41 (d, *J* = 16.0 Hz, 1H), 4.35 (d, *J* = 11.3 Hz, 1H), 3.94 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 165.0, 141.3, 133.7, 133.3, 131.8, 131.5, 130.6, 130.0, 129.9, 128.7, 127.8, 127.1, 124.2, 122.2, 122.0, 83.6, 57.6, 50.0, 37.9; HRMS (ESI) calcd for $C_{26}H_{17}Br_3F_6O_3Na$ *m*/*z* $[M + Na]^+$ 750.8530, found 750.8545.

*1,4,4-Tribromo-2-(3-chlorophenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3f**).* Yellow oil (10.1 mg, 81% yield); IR (KBr) 3089, 2856, 1768, 1654, 1523, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.11 (dd, *J* = 8.2, 1.0 Hz, 2H), 7.92 (dd, *J* = 8.3, 1.0 Hz, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.54−7.45 (m, 3H), 7.43 (d, *J* = 1.8 Hz, 1H), 7.40−7.28 (m, 5H), 4.71 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 4.33 (d, *J* = 15.8 Hz, 1H), 3.93 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 165.0, 140.5, 134.5, 133.4, 133.0, 132.4, 130.6, 130.4, 129.9, 129.6, 128.5, 128.4, 127.7, 126.9, 124.8, 83.8, 58.8, 50.6, 38.7; HRMS (ESI) calcd for $C_{24}H_{18}Br_3ClO_3Na$ *m*/*z* $[M + Na]^+$ 648.8392, found 648.8381.

*1,4,4-Tribromo-2-(4-nitrophenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3g**).* Yellow oil (9.8 mg, 77% yield); IR (KBr) 3021, 1745, 1685, 1561, 954, 798 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.8 Hz, 2H), 8.10 (d, *J* = 7.4 Hz, 2H), 7.94 (d, *J* = 7.6 Hz, 2H), 7.68 (d, *J* = 8.8 Hz, 2H), 7.63 (t, *J* = 7.5 Hz, 1H), 7.57−7.42 (m, 3H), 7.36 (t, *J* = 7.8 Hz, 2H), 4.77 (d, *J* = 11.2 Hz, 1H), 4.37 (dd, *J* = 17.1, 13.6 Hz, 2H), 3.97 (d, *J* = 15.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1, 165.0, 147.5, 145.8, 133.6, 133.3, 131.9, 130.7, 130.1, 129.9, 128.6, 127.8, 127.7, 123.4, 83.9, 58.1, 50.3, 38.3; HRMS (ESI) calcd for $C_{24}H_{18}Br_3NO_5Na$ *m*/*z* $[M + Na]^+$ 659.8633, found 659.8676.

*1,4,4-Tribromo-2-(4-methoxyphenyl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3h**).* Yellow oil (10.2 mg, 82% yield); IR (KBr) 2634, 1795, 1611, 1527, 1231, 765 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.17−8.05 (m, 2H), 7.93−7.81 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.46 (dd, *J* = 14.2, 6.5 Hz, 3H), 7.39−7.27 (m, 4H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.70 (d, *J* = 11.0 Hz, 1H), 4.43 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 3.96 (d, *J* = 15.7 Hz, 1H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.3, 165.1, 159.3, 133.2, 132.8, 132.5, 130.7, 130.5, 129.9, 129.8, 128.4, 127.8, 127.6, 113.7, 84.3, 59.9, 55.2, 51.2, 39.2; HRMS (ESI) calcd for $C_{25}H_{21}Br_3O_4Na$ *m*/*z* $[M + Na]^+$ 644.8888, found 644.8856.

*1,4,4-Tribromo-5-oxo-5-phenyl-2-(m-tolyl)pentan-2-yl Benzoate (**3i**).* Yellow oil (10.3 mg, 85% yield); IR (KBr) 3081, 1758, 1664, 1302, 945, 717 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.20−8.09 (m, 2H), 7.85 (d, *J* = 7.6 Hz, 2H), 7.59 (t, *J* = 7.4 Hz, 1H), 7.47 (q, *J* = 7.9 Hz, 3H), 7.34 (t, *J* = 7.8 Hz, 2H), 7.22 (d, *J* = 5.1 Hz, 2H), 7.18−7.09 (m, 2H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.47 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 15.7 Hz, 1H), 3.97 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 165.1, 138.0, 138.0, 133.2, 132.7, 132.6, 130.7, 130.5, 130.0, 129.0, 128.4, 128.3, 127.6, 127.0, 123.6, 84.4, 59.8, 51.3, 39.1, 21.7; HRMS (ESI) calcd for $C_{25}H_{21}Br_3O_3Na$ *m*/*z* $[M + Na]^+$ 628.8939, found 628.8954.

*1,4,4-Tribromo-5-oxo-5-phenyl-2-(thiophen-3-yl)pentan-2-yl Benzoate (**3j**).* Yellow oil (9.9.mg, 83% yield); IR (KBr) 3041, 1756, 1612, 1172, 977, 712 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.16−8.04 (m, 2H), 7.92 (dd, *J* = 8.4, 1.1 Hz, 2H), 7.58 (dd, *J* = 10.6, 4.3 Hz, 1H), 7.54−7.41 (m, 3H), 7.40−7.32 (m, 3H), 7.29 (dd, *J* = 5.1, 3.0 Hz, 1H), 7.04 (dd, *J* = 5.1, 1.4 Hz, 1H), 4.68 (d, *J* = 11.0 Hz, 1H), 4.39 (d, *J* = 11.0 Hz, 1H), 4.34 (d, *J* = 15.7 Hz, 1H), 3.95 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 188.4, 165.1, 139.2, 133.2, 132.8, 132.6, 130.6, 130.5, 129.9, 128.4, 127.6, 126.5, 125.7, 123.6, 83.3, 59.2, 50.7, 38.8; HRMS (ESI) calcd for $C_{22}H_{17}Br_3SO_3Na$ *m*/*z* $[M + Na]^+$ 620.8346, found 620.8358.

*1,4,4-Tribromo-2-(naphthalene-2-yl)-5-oxo-5-phenylpentan-2-yl Benzoate (**3k**).* Yellow oil (10.3 mg, 80% yield); IR (KBr) 3075, 1759, 1669, 1308, 1154, 921 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.2 Hz, 2H), 7.89 (s, 1H), 7.82 (dd, *J* = 13.3, 8.4 Hz, 2H), 7.76 (d, *J* = 7.9 Hz, 1H), 7.66−7.59 (m, 1H), 7.57 (d, *J* = 8.3 Hz, 2H), 7.55−7.45 (m, 5H), 7.38 (td, *J* = 7.5, 0.9 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 2H), 4.85 (d, *J* = 11.0 Hz, 1H), 4.58 (d, *J* = 11.0 Hz, 1H), 4.44 (d, *J* = 15.7 Hz, 1H), 4.08 (d, *J* = 15.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4, 165.2, 135.5, 133.3, 132.8, 132.6, 132.4, 130.7, 130.3, 130.0, 128.5, 128.5, 128.1, 127.4, 126.7, 126.4, 126.1, 123.9, 84.5, 59.6, 51.1, 38.9; HRMS (ESI) calcd for $C_{28}H_{21}Br_3O_3Na$ *m*/*z* $[M + Na]^+$ 664.8939, found 664.8956.

*1,4,4-Tribromo-2-methyl-5-oxo-5-phenylpentan-2-yl Benzoate (**3l**).* Yellow oil (7.9 mg, 75% yield); IR (KBr) 3080, 2275, 1764, 1358, 1282, 1187 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.33−8.09 (m, 2H), 7.99 (dd, *J* = 8.3, 1.1 Hz, 2H), 7.66−7.49 (m, 2H), 7.45 (dd, *J* = 10.8, 4.9 Hz, 2H), 7.39 (t, *J* = 7.8 Hz, 2H), 4.14 (d, *J* = 10.6 Hz, 1H), 4.00 (dd, *J* = 13.3, 5.1 Hz, 2H), 3.79 (d, *J* = 16.0 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.4, 165.4, 133.2, 133.0, 132.6, 130.9, 130.8, 129.8, 128.3, 128.0, 82.2, 59.5, 50.2, 39.7, 23.4; HRMS (ESI) calcd for $C_{19}H_{17}Br_3O_3Na$ *m*/*z* $[M + Na]^+$ 552.8626, found 552.8642.

*1,4,4-Tribromo-5-(4-chlorophenyl)-5-oxo-2-phenylpentan-2-yl 4-Chlorobenzoate (**5a**).* Yellow oil (10.3 mg, 78% yield); IR (KBr) 3097, 1735, 1671, 1308, 1107, 791 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.14−7.97 (m, 2H), 7.92−7.71 (m, 2H), 7.47−7.43 (m, 2H), 7.42−7.38 (m, 2H), 7.37−7.33 (m, 3H), 7.33−7.29 (m, 2H), 4.68 (d, *J* = 11.1 Hz, 1H), 4.44 (d, *J* = 11.1 Hz, 1H), 4.30 (d, *J* = 15.8 Hz, 1H), 3.92 (d, *J* = 15.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3, 164.2, 139.9, 139.3, 137.8, 132.0, 131.3, 130.7, 129.1, 128.9, 128.5, 128.3, 128.0, 126.4, 84.6, 58.7, 50.9, 39.0; HRMS (ESI) calcd for $C_{24}H_{17}Br_3Cl_2O_3Na$ *m*/*z* $[M + Na]^+$ 682.8003, found 682.8014.

*1,4,4-Tribromo-5-(4-methoxyphenyl)-5-oxo-2-phenylpentan-2-yl 4-Methoxybenzoate (**5b**).* Yellow oil (10.7 mg, 82% yield); IR (KBr) 3077, 1743, 1643, 1587, 984, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.08 (d, *J* = 8.7 Hz, 2H), 7.99 (d, *J* = 9.0 Hz, 2H), 7.43 (dd, *J* = 7.6, 1.6 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 3H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 9.0 Hz, 2H), 4.68 (d, *J* = 10.9 Hz, 1H), 4.42 (d, *J* = 10.9 Hz, 1H), 4.32 (d, *J* = 15.8 Hz, 1H), 3.96 (d, *J* = 15.8 Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 186.6, 164.8, 163.6, 163.2, 138.5, 133.3, 132.1, 128.2, 128.1, 126.5, 124.5, 123.1, 113.7, 112.9, 84.1, 59.8, 55.4, 51.2, 39.5; HRMS (ESI) calcd for $C_{26}H_{23}Br_3O_5Na$ *m*/*z* $[M + Na]^+$ 674.8993, found 674.8978.

*1,4,4-Tribromo-6,6-dimethyl-5-oxo-2-phenylheptan-2-yl Pivalate (**5c**).* Yellow oil (9.4 mg, 85% yield); IR (KBr) 3061, 1695, 1661, 1202, 907, 777 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.40−7.26 (m, 5H), 4.65 (d, *J* = 10.9 Hz, 1H), 4.23 (d, *J* = 10.9 Hz, 1H), 4.03 (d, *J* = 15.8 Hz, 1H), 3.80 (d, *J* = 15.8 Hz, 1H), 1.36 (s, 9H), 1.23 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 199.3, 176.9, 137.3, 127.9, 127.9, 127.2, 83.9, 58.6, 50.6, 45.7, 39.9, 39.5, 29.4, 27.5; HRMS (ESI) calcd for $C_{20}H_{27}Br_3O_3Na$ *m*/*z* $[M + Na]^+$ 574.9408, found 574.9421.

*(3-Bromo-5-(bromomethyl)-2-methoxy-2,5-diphenyltetrahydrofuran-3-yl)(phenyl)methanone (**6**).* (Major isomer) colorless oil (8.0 mg, 76% yield); IR (KBr) 3040, 1887, 1623, 1518, 1410, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.68 (td, *J* = 8.5, 1.2 Hz, 4H), 7.49 (dd, *J* = 8.4, 7.2 Hz, 3H), 7.43−7.33 (m, 3H), 7.33−7.24 (m, 5H), 3.90 (d, *J* = 14.8 Hz, 1H), 3.82−3.66 (m, 2H), 3.49 (d, *J* = 14.8 Hz, 1H), 3.29 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 193.2, 142.9, 137.3, 134.2, 131.9, 129.8, 129.0, 127.9, 127.8, 127.6, 126.9, 125.8, 112.6, 104.9,

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84.3, 70.5, 51.7, 50.5, 44.2; HRMS (ESI) calcd for $C_{25}H_{22}Br_2O_3Na$ *m*/*z* [M + Na]$^+$ 550.9833, found 550.9845.

*4,4-Dibromo-5-oxo-2,5-diphenylpentan-2-yl Benzoate (**9**).* Yellow oil (9.5 mg, 92% yield); IR (KBr) 3080, 1792, 1633, 1375, 1140, 979 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (dd, *J* = 8.4, 1.2 Hz, 2H), 8.05 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.60−7.49 (m, 2H), 7.46−7.37 (m, 5H), 7.36−7.30 (m, 2H), 7.30−7.27 (m, 1H), 3.86 (dd, *J* = 35.0, 15.8 Hz, 2H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.3, 164.8, 144.2, 132.9, 132.9, 132.8, 131.2, 130.8, 129.7, 128.5, 128.3, 127.8, 127.4, 124.8, 84.4, 60.3, 56.0, 24.6; HRMS (ESI) calcd for $C_{24}H_{20}Br_2O_3Na$ *m*/*z* [M + Na]$^+$ 536.9677, found 536.9654; HPLC (Daicel Chiralpak ID, *i*-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm) t_1 = 13.1 min (minor), t_2 = 16.5 min (major).

C. Oxidation of 3a. The procedure was modified based on Prof. David Procter's report.[12c] An oven-dried Schlenk flask (10 mL) with a stir bar was placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Samarium(II) iodide (0.1 M THF solution, prepared in situ, 0.01 mmol, 1 equiv) was added followed by H_2O (0.02 mmol, 2 equiv) (fully degassed by bubbling argon) with vigorous stirring. The dibromo substrate **3a** (0.01 mmol) was added, and the reaction mixture was vigorously stirred under argon. After TLC monitored the total consumption of starting dibromo compound, the reaction mixture was rapidly quenched by bubbling of air though the reaction mixture. The reaction mixture was diluted with CH_2Cl_2 (5 mL) and H_2O (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 8 mL); the organic layers were combined, dried over Na_2SO_4, filtered, concentrated, and purified by flash column chromatography with eluent hexanes/ethyl acetate = 100/5 to yield the corresponding product **10**.

*1-Bromo-4,5-dioxo-2,5-diphenylpentan-2-yl Benzoate (**10**).* Colorless oil (3.4 mg, 76% yield); IR (KBr) 3120, 1786, 1720, 1698, 1480, 951, 782 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.13−7.98 (m, 2H), 7.79−7.68 (m, 2H), 7.64−7.51 (m, 2H), 7.51−7.41 (m, 4H), 7.40−7.27 (m, 5H), 4.62 (d, *J* = 10.9 Hz, 1H), 4.41 (d, *J* = 11.0 Hz, 1H), 4.33 (d, *J* = 16.5 Hz, 1H), 4.02 (d, *J* = 16.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.0, 190.3, 139.4, 134.4, 133.3, 130.3, 129.8, 128.6, 128.5, 128.4, 128.4, 125.3, 82.2, 45.0, 38.3; HRMS (ESI) calcd for $C_{24}H_{19}BrO_4Na$ *m*/*z* [M + Na]$^+$ 473.0364, found 473.0376.

D. Application Synthesis of Trisubstituted THF Ring. *(5-(Bromomethyl)-2,5-diphenyltetrahydrofuran-3-yl)(phenyl)-methanone (**2**).* A solution of **1** (42 mg, 0.1 mmol, 1.0 equiv), TBAI (37 mg, 0.1 mmol, 1 equiv), and triethylsilane (320 μL, 2 mmol, 20 equiv) in dichloromethane (2 mL) was stirred at 0 °C for 10 min. A solution of trifluoroacetic acid (80 μL, 1 mmol, 10 equiv) in CH_2Cl_2 (1 mL) was slowly added to the reaction mixture over 10 min. The solution was further stirred for 1 h at 0 °C (total consumption of starting material as indicated by TLC) and quenched with saturated aqueous $NaHCO_3$ solution (15 mL). The mixture was extracted with CH_2Cl_2 (5 mL × 3). The combined organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was subjected to flash column chromatography to give the desired product **2** (38 mg, 92%).

Colorless oil; $[\alpha]_D^{25}$ +63 (*c* 1.0, $CHCl_3$, 94% ee); IR (KBr) 1553, 1451, 1398, 1291, 1128, 811 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82−7.70 (m, 2H), 7.66−7.57 (m, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.49−7.45 (m, 2H), 7.40−7.27 (m, 8H), 5.30 (d, *J* = 9.6 Hz, 1H), 4.35 (q, *J* = 11.0 Hz, 1H), 3.78 (q, *J* = 11.0 Hz, 2H), 3.16 (dd, *J* = 12.7, 9.1 Hz, 1H), 2.74 (dd, *J* = 12.7, 10.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 198.4, 144.0, 139.6, 136.6, 133.3, 128.6, 128.5, 128.4, 128.3, 128.1, 127.8, 126.6, 125.3, 84.8, 83.1, 56.7, 43.6, 43.3; HRMS (ESI) calcd for $C_{24}H_{21}O_2BrNa$ *m*/*z* [M + Na]$^+$ 443.0623, found 443.0619; HPLC (Daicel Chiralpak IE, *i*-PrOH/hexane = 15/85, 0.6 mL/min, 254 nm) t_1 = 10.1 min (major), t_2 = 12.5 min (minor).

■ ASSOCIATED CONTENT

Supporting Information

CIF file of **3a**, HPLC chromatograms, X-ray structure of **3a**, and NMR spectra. 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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(7) For details, see the Supporting Information.

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(9) We also conducted the ring opening reaction using enantioenriched **1b**, **1c**, **1d**, and **1h** as the substrates with either NBS or NCS as the halogen source. High yields of the desired products were obtained without ee erosion.

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