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Stereoselective construction of multi-substituted tetrahydrofurans via three components-condensation reaction

Akio Kamimura,[a,*] Hiromasa Mitsudera,[a] Kenji Matsuura,[a] Yoji Omata,[a] Masashi Shirai,[b] Shuji Yokoyama[b] and Akikazu Kakehi[c]

[a]*Department of Applied Chemistry, Faculty of Engineering, Yamaguchi University, Ube 755-8611, Japan*
[b]*Ube Laboratory, Ube Industries Ltd., Ube 755-8633, Japan*
[c]*Department of Material Engineering and Chemistry, Faculty of Engineering, Shinshu University, Nagano 380-8551, Japan*

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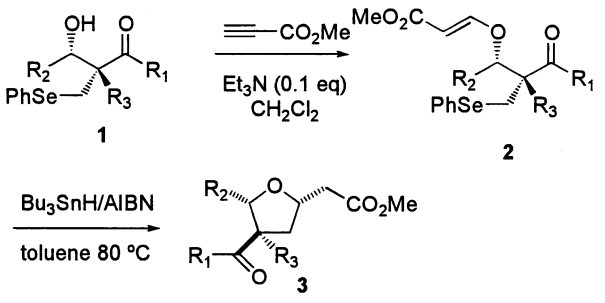
Abstract—Stereoselective construction of multi-substituted tetrahydrofurans is described. The procedure is consisted in three steps: stereoselective Michael/aldol tandem reaction, alkenylation, and radical cyclization. A chiral or racemic adduct of the tandem Michael/aldol reaction, β-hydroxyl-α-(phenylseleno)alkyl carbonyl compound, was alkenylated by treatment with propiolic ester to give a precursor of radical cyclization in good yields. Exposure of the precursor to Bu_3SnH in hot toluene gave tri- or tetrasubstituted tetrahydrofurans in a good yield. The good control of relative configuration between C2 and C3 during the tandem reaction stage and the excellent 2,5-*cis*-induction in the radical cyclization brought the stereoselective formation of trisubstituted tetrahydrofurans. A prochiral radical carbon generated from a secondary selenide attacked the double bond in a stereoselective manner and one of four possible diastereomers of tetrahydrofuran was formed stereoselectively.

1. Introduction

Tetrahydrofuran units are very often seen among natural products such as antibiotics and *C*-glycosides.[1] The formation of the ring has been attracting many organic chemists so far and a number of effective methodologies to construct it have been developed.[2,3] Recently, we[4] and others[5] have reported a facile method to prepare β-hydroxyl-α-alkylseleno ketones, esters or amides **1**, potentially useful synthetic building blocks, in one step from an α,β-unsaturated carbonyl compound, an aldehyde and a selenolate. With use of chiral acyloxy borane,[6] the ketone derivatives were prepared in a highly enantioselective way.[4a] We were interested in developing a new use of the tandem adducts in organic synthesis, and paid our attention on radical chemistry,[7] which are regarded as a powerful tool to access cyclic compounds under neutral reaction conditions.[8] The cyclization process usually requires both a radical precursor unit, such as halogen or charcogen, and a radical acceptor unit, usually alkene, in proper position. Preparation of such precursors sometimes causes problems. Our tandem adduct already possesses a phenylseleno group that works as the radical source[9] so that the cyclization would be easily accomplished if the radical acceptor unit was installed. In this paper, we report a new stereoselective preparation of tri or tetrasubstituted tetrahydrfurans from an α,β-unsaturated carbonyl compound, an aldehyde and a methyl propiolate, in three steps of manipulation.

2. Results and discussion

The tandem adducts **1** were prepared in the previously reported method.[4] Compounds **1a**–**1e** were prepared in optically active form via catalytic asymmetric tandem reaction,[4a] while compounds **1f**–**1h** were obtained in racemic form.[4b,c] Conversion of **1** to radical precursor **2** was carried out by treatment with methyl propiolate in the presence of catalytic amount of base (Scheme 1).[10] Precursors were



Scheme 1.

Keywords: radicals and radical reactions; furans; stereoselection; Michael reactions; Aldol reactions.

* Corresponding author. Tel.: +81-836-35-9231; fax: +81-836-35-9201; e-mail: ak10@yamaguchi-u.ac.jp

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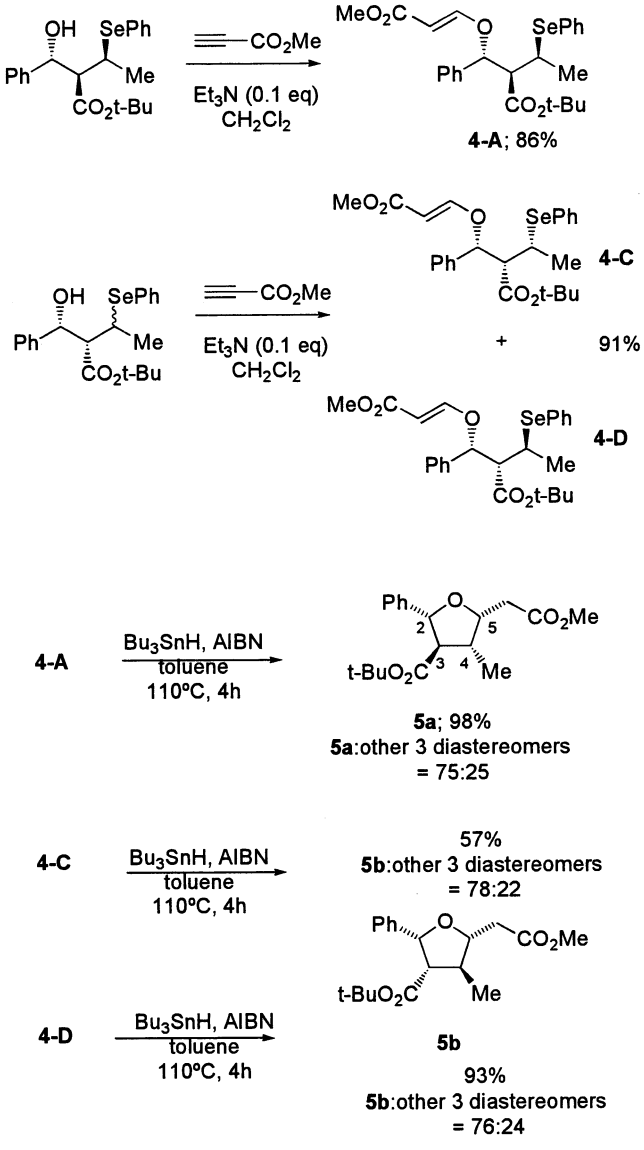
Table 1. Preparation of Tetrahydrofuran **3**

Entry	R^1	R^2	R^3	**1**	ee[a]	**2**	Yield (%)[b]	**3**	Yield (%)[b]	$[\alpha]_D$
1	Me	Me	H	**1a**	91	**2a**	77	**3a**	85	−13.1
2	Et	Me	H	**1a**	84	**2b**	83	**3b**	83	−18.9
3	Me	Pr-*i*	H	**1a**	89	**2c**	67	**3c**	59	−15.9
4	Me	Bu	H	**1a**	92	**2d**	80	**3d**	81	−24.3
5	Me	Ph	H	**1a**	49	**2e**	91	**3e**	59	−23.8
6	OBu-*t*	Ph	H	**1a**	–[c]	**2f**	88	**3f**	95	–
7	OBu-*t*	*p*-Cl-C_6H_4-	H	**1a**	–[c]	**2g**	93	**3 g**	86	–
8	OBu-*t*	Ph	Me	**1a**	–[c]	**2h**	54	**3 h**	99	–

[a] Determined by HPLC analyses with Chiralcel OD-H.
[b] Isolated yield.
[c] Racemic.

purified in diastereomerically pure form during the conversion to **2**, which was exposed to Bu_3SnH in hot toluene under the standard conditions. The results are summarized in Table 1.

Treatment of **2a**, for example, with Bu_3SnH in the presence of catalytic amounts of AIBN smoothly gave desired tetrahydrofuran **3a** in 85% yield (entry 1). The crude reaction mixture indicated **3a** was formed in almost single isomer so that the cyclization occurred in a highly stereoselecive manner. Other optically active precursors **2** also underwent the stereoselective conversion to **3** on treatment with Bu_3SnH (entry 2–5). A tetrahydrofuran containing a quaternary carbon was also synthesized stereoselectively from radical precursor **2h** (entry 8). Thus, the present tandem Michael/aldol-radical cyclization method provides a short-step and useful preparation of trisubstituted tetrahydrofuran derivatives.

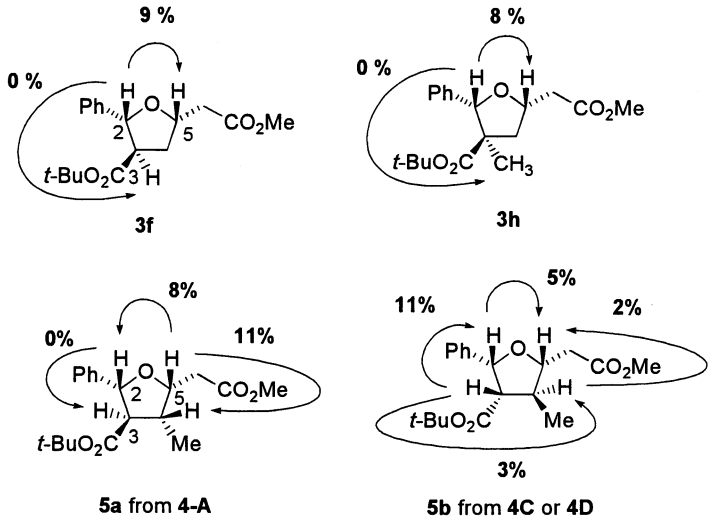


Scheme 2.

We next applied the present method to the formation of tetrasubstituted tetrahydrofuran (Scheme 2).[4d] The precursor of the cyclization was prepared in a similar manner to the method mentioned above except for starting from *tert*-butyl crotonate. Three out of four possible diastereomers of the radical precursor **4** were prepared selectively by proper choice of counter cation of selenolate. Thus, diastereomer **4-A** was obtained from the reaction with lithium selenolate followed by alkenylation,[4c] while a mixture of **4-C** and **4-D**, which held *anti*-aldol configuration, was prepared through the reaction with magnesium selenolate.[4d] Compounds **4-C** and **4-D** were separated by careful chromatographic treatment. Each isomer of **4** was used the next stage, radical cyclization (Scheme 2).

The reaction of **4-A** resulted in the formation of tetrasubstituted tetrahydrofuran **5a** in 98% yield. The NMR spectrum of the products showed that four diastereomers of **5** was contained in the crude mixture, in which one of the isomer, **5a**, was formed as the major component in the ratios of 75:16:4:5. This set of value reflects that the major isomer **5a** was formed in 75:25 selectivity. Other isomers **4-C** and **4-D** were also converted to **5** in good yields. In these reactions, **5b** was isolated as the major isomer in a similar ratio. Thus, the present method provides a simple way to obtain tetrasubstituted tetrahydrofuran in a stereoselective manner.

The stereochemistry of the cyclized products were determined in the following way. Scheme 3 shows the results for NOE experiments performed with trisubstituted tetrahydrofurans **3f** and **3h**. Irradiation of H2 nuclei in **3f**, for example, enhanced the H5 signal by 9% but H3 by 0%. A similar trend was also observed in compound **3h**. These results clearly suggest that H2 and H5 occupy in the same



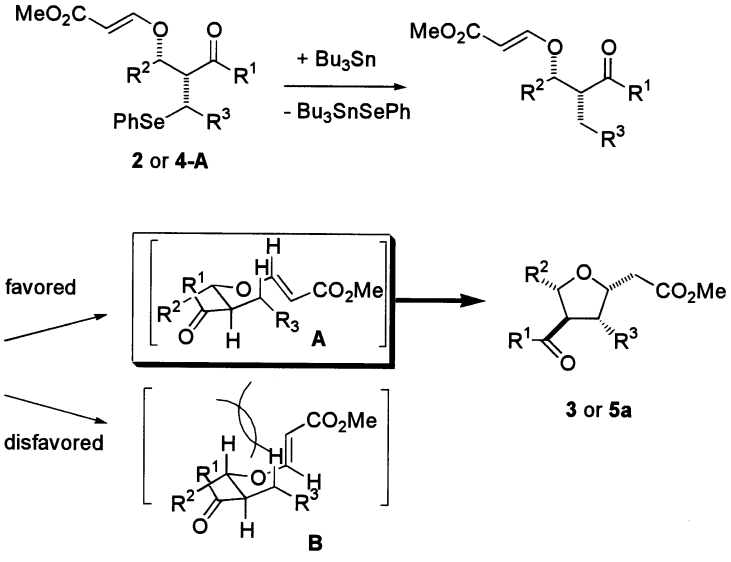
Scheme 3. The results of NOE experiments.

side of the ring, i.e. 2,5-*cis*, and H3 or C3-Me is located the other side, i.e. 2,3-*trans*. Compared with the known results of other radical cyclization, the present conclusion was reasonable.[3g]

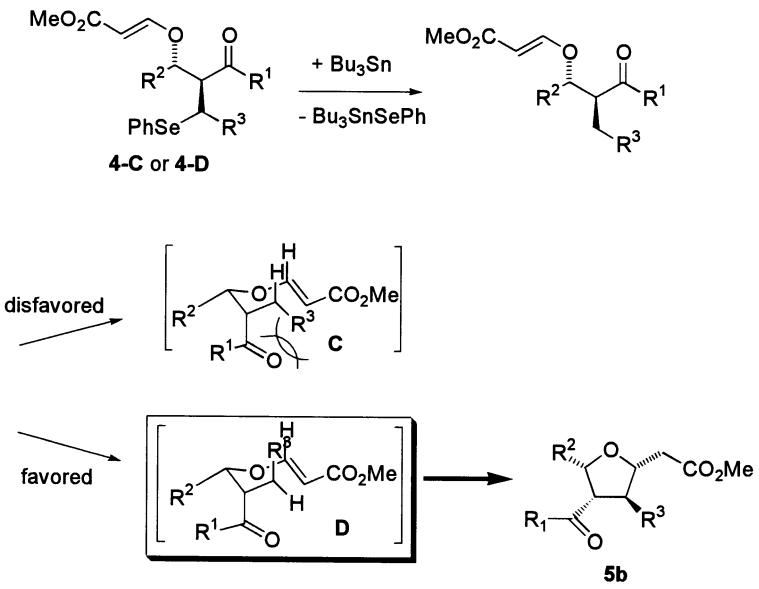
Structural elucidation of tetrasubstituted tetrahydrofuran **5** was assisted with an X-ray crystallographic analysis. Recrystallization of the cyclized product from **4**-**C** gave diastereomerically pure **5b** in crystal form. An X-ray analysis for this crystal unambiguously indicated the configuration of **5b** as shown in Scheme 3, in which 2,5-*cis* relationship was again observed.[11] Based on this information, we performed NOE experiments for **5a** and **5b**. Irradiation on H5 in **5a** brought 11% signal enhancement for H4 and 8% for H2. These results suggest that **5a** has *cis*-configuration between H4 and H5 and we determined the structure of **5a** as shown in Scheme 3.

The configuration between C2 and C3 in tetrahydrofuran **3** or **5** depends on the stereoselectivity of the tandem reaction step. The radical cyclization takes place with high 2,5-*cis* induction which accomplishes stereoselective formation of trisubstituted tetrahydrofurans. The high stereoselectivity of the radical cyclization should be explained in the following way. The radical intermediate should have two conformers **A** and **B** (Scheme 4). In conformer **A**, all substituents occupy pseudo-equatorial positions, while in conformer **B**, the alkenyl group, the radical acceptor, is located in pseudo axial position that causes steric repulsion. As a result, conformer **A** should be much favorable than conformer **B** and the ring enclosure takes place through **A** to give 2,5-*cis* tetrahydrofurans.

For the formation of tetrasubstituted derivatives **5**, 2,5-*cis* relationship was also observed during the ring formation. This suggests that a similar transition structure can be applied to these reactions. During the formation of **5**, the radical center, C4, becomes prochiral that may generate four diastereomers during the addition to prochiral C5 sp^2 carbon. The cyclization from **4**-**A**, which has the same



Scheme 4.



Scheme 5.

2,3-*syn* relationship as **2**, should go through a similar reaction pathway as shown in Scheme 4. To avoid the streic repulsion caused by the alkenyl acceptor, R^3 should favor the pseudo-equatorial position in **A** and R^3 group is located to *cis* to C5 carbon to give **5a**. On the other hand, due to *anti*-2,3 configuration, the cyclization of **4-C** and **4-D** requires the *tert*-butoxycarbonyl group occupying pseudo-axial (Scheme 5). R^3 group probably avoids the steric repulsion caused by the *tert*-butyl ester group and likely favors the *trans* position to the group (conformer **D**), giving **5b** in a stereoselective manner.

In conclusion, the present methodology provides a convenient preparation of tri- or tetrasubstituted tetrahydrofuran derivatives stereoselectively in a short process from α,β-unsaturated compound, aldehyde and propiolate ester. Combination of stereoselectivity from the tandem reaction and the following radical cyclization will open versatile applicability for the synthesis of tetrahydrofuran derivatives.

3. Experimental

3.1. General

^1H and ^{13}C NMR spectra were measured in $CDCl_3$ and recorded on Hitachi R-250H (250 MHz for ^1H and 62.5 MHz for ^{13}C), JEOL EX-270 (270 MHz for ^1H and 67.5 MHz for ^{13}C), or Brucker Advance 400 (400 MHz for ^1H and 100 MHz for ^{13}C) spectrometer. Specific rotation was measured by Horiba SEPA-2000 polarimeter at 589 nm. All the reactions in this paper were performed under nitrogen atmosphere. Solvents were dried over appropriate drying agents (Na for toluene and CaH_2 for CH_2Cl_2) and distilled under nitrogen before use. Bu_3SnH, methyl propiolate, and AIBN were purchased from Aldrich or TCI, and used without further purification. Compounds **1** were prepared in previously reported results.[4]

3.1.1. Preparation of *O*-alkenylated precursors of the cyclization. Preparation of methyl 3-[(1*S*,2*S*)-1-methyl-3-oxo-2-phenylselanylmethylbutoxy]acrylate (2a). General procedure. To a solution of **1a** (384.3 mg, 1.41 mmol) in CH_2Cl_2 was added methyl propiolate (137.4 mg, 1.64 mmol) and *N*-methylmorpholine (11.3 mg, 0.11 mmol) and the reaction mixture was allowed to stand at room temperature for 18 h. After removal of solvent in vacuo, the residue was purified through flash chromatography (silica gel/hexane–ethyl acetate 10:1 v/v then 5:1 v/v) to give **2a** in 77% yield (388.7 mg). Colorless oil. $[\alpha]_D=-42.6°$ (*c* 0.80, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.43 (d, 1H, *J*=16.4 Hz), 7.24–7.60 (m, 5H), 5.28 (d, 1H, *J*=15.6 Hz), 4.27 (quint, 1H, *J*=6.1 Hz), 3.69 (s, 3H), 2.98–3.11 (m, 3H), 2.19 (s, 3H), 1.20 (d, 3H, *J*=6.4 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 211.1, 167.9, 160.9, 133.2, 129.4, 127.6, 104.1, 98.4, 79.5, 57.1, 51.1, 32.3, 25.1, 17.3. Exact mass determination: 356.0497 (calcd $C_{16}H_{20}O_4Se$: 356.0527).

3.1.2. Methyl 3-[(1*S*,2*S*)-1-methyl-3-oxo-2-phenylselanylmethylpentyloxy]-acrylate (2b). $[\alpha]_D=-35.6°$ (*c* 1.33, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.44 (d, 1H, *J*=15.0 Hz), 7.21–7.60 (m, 5H), 5.27 (d, 1H, *J*=12.5 Hz), 4.24 (quint, 1H, *J*=6.1 Hz), 3.74 (s, 3H), 2.99–3.11 (m, 3H), 2.47 (q, 2H, *J*=7.3 Hz), 1.18 (d, 3H, *J*=6.1 Hz), 1.00 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 211.2, 168.5, 161.4, 133.5, 129.9, 128.0, 104.6, 98.8, 80.3, 56.9, 51.7, 39.5, 25.9, 17.9, 7.8. Exact mass determination: 370.0694 (calcd $C_{17}H_{22}O_4Se$: 370.0683).

3.1.3. Methyl 3-[(1*S*,2*S*)-1-isopropyl-3-oxo-2-phenylselanylmethylbutoxy]-acrylate (2c). $[\alpha]_D=-5.4°$ (*c* 0.58, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 (d, 1H, *J*=12.2 Hz), 7.27–7.55 (m, 5H), 5.30 (d, 1H, *J*=12.2 Hz), 3.89 (dd, 1H, *J*=4.9, 6.7 Hz), 3.68 (s, 3H), 3.08–3.15 (m, 3H), 2.32 (s, 3H), 1.76–1.83 (m, 1H), 0.88 (d, 3H, *J*=6.7 Hz), 0.85 (d, 3H, *J*=6.7 Hz). Exact mass determination: 384.0846 (calcd $C_{18}H_{24}O_4Se$: 384.0840).

3.1.4. Methyl 3-[(1*S*)-1-(2-oxo-1-phenylselanylmethyl-propyl)pentyloxy]acrylate (2d). $[\alpha]_D=-21.3°$ (*c* 0.60, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.46 (d, 1H, *J*=12.5 Hz), 7.26–7.60 (m, 5H), 5.32 (d, 1H, *J*=12.5 Hz), 4.10 (q, 1H, *J*=6.4 Hz), 3.70 (s, 3H), 2.96–3.11 (m, 3H), 2.18 (s, 3H), 1.24–1.62 (m, 6H), 0.84 (t, 3H, *J*=7.0 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 207.1, 167.2, 161.3, 132.5, 128.7, 126.9, 103.3, 97.3, 83.7, 55.4, 50.4, 30.9, 30.7, 26.8, 24.2, 21.7, 13.2. Exact mass determination: 398.0977 (calcd $C_{19}H_{26}O_4Se$: 398.0996).

3.1.5. Methyl 3-[(1*S*,2*S*)-3-oxo-1-phenyl-2-phenylselanyl-methylbutoxy]acrylate (2e). $[\alpha]_D=+22.7°$ (*c* 0.85, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.15–7.43 (m, 11H), 5.20 (d, 1H, *J*=12.5 Hz), 4.95 (d, 1H, *J*=8.2 Hz), 3.62 (s, 3H), 3.15–3.34 (m, 3H), 1.78 (s, 3H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 209.0, 167.6, 160.5, 160.4, 137.2, 132.6, 129.1, 129.0, 127.3, 126.9, 99.5, 85.7, 84.5, 59.5, 51.1, 32.4, 24.8. Anal. calcd for $C_{21}H_{22}O_4Se$: C, 60.43; H, 5.31%. Found: C, 60.09; H, 5.35. Exact mass determination: 418.0678 (calcd $C_{21}H_{22}O_4Se$: 418.0683).

3.1.6. Methyl 3-(2-*tert*-butoxycarbonyl-1-phenyl-3-phenylselanylpropoxy)-acrylate (2f). ^1H NMR (270 MHz, $CDCl_3$) δ 7.41 (d, 1H, *J*=12.2 Hz), 7.16–7.38 (m, 10H), 5.22 (d, 1H, *J*=12.5 Hz), 5.06 (d, 1H, *J*=7.6 Hz), 3.63 (s, 3H), 3.25 (dd, 1H, *J*=4.0, 12.2 Hz), 3.17 (dd, 1H, *J*=9.9, 11.9 Hz), 3.06 (ddd, 1H, *J*=4.0, 7.6, 9.6 Hz), 1.25 (s, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.8, 167.7, 160.7, 136.8, 132.7, 132.4, 129.0, 128.8, 128.6, 126.9, 126.9, 98.9, 84.7, 81.8, 54.2, 51.0, 27.7, 24.9. Anal. calcd for $C_{24}H_{28}O_5Se$: C, 60.63; H, 5.94%. Found C, 60.62; H, 5.96. Exact mass determination: 476.1125 (calcd $C_{24}H_{28}O_5Se$: 476.1102).

3.1.7. Methyl 3-[2-*tert*-butoxycarbonyl-1-(4-chloro-phenyl)-3-phenylselanyl-propoxy]acrylate (2g). ^1H NMR (270 MHz, $CDCl_3$) δ 7.14–7.42 (m, 10H), 5.21 (d, 1H, *J*=12.5 Hz), 5.04 (d, 1H, *J*=7.9 Hz), 3.63 (s, 3H), 3.19 (d, 1H, *J*=4.3 Hz), 3.11 (d, 1H, *J*=8.6 Hz), 3.01 (ddd, 1H, *J*=4.3, 7.9, 9.5 Hz), 1.27 (s, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.7, 167.5, 160.4, 135.5, 134.6, 132.7, 129.1, 128.4, 128.3, 127.3, 127.1, 99.2, 83.8, 82.0, 51.1, 28.0, 27.7, 25.1. Exact mass determination: 510.0689 (calcd $C_{24}H_{27}ClO_5Se$: 510.0712).

3.1.8. Methyl 3-(2-*tert*-butoxycarbonyl-2-methyl-1-phenyl-3-phenylselanyl-propoxy)-acrylate (2h). ^1H NMR (270 MHz, $CDCl_3$) δ 7.18–7.45 (m, 10H), 5.28 (s, 1H), 5.16 (d, 1H, *J*=3.5 Hz), 3.61 (s, 3H), 3.49 (d, 1H, *J*=11.9 Hz), 2.99 (d, 1H, *J*=11.9 Hz), 1.43 (s, 9H), 1.21 (s, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.0, 167.8, 161.0 135.4, 135.4, 132.6, 131.9, 128.7, 128.3, 127.8, 126.8, 98.9, 87.4, 82.2, 51.1, 34.2, 27.9, 18.3, 14.1. Anal. calcd for $C_{25}H_{30}O_5Se$: C, 61.35; H, 6.18%. Found: C, 61.31; H, 6.26. Exact mass determination: 490.1238 (calcd $C_{25}H_{30}O_5Se$: 490.1258).

3.2. Radical cyclization. Preparation of (3-acetyl-5-(methoxycalbonyl)methy-2-methyltetrahydrofuran (3a). General procedure

A mixture of **2a** (157.2 mg, 0.44 mmol), Bu_3SnH (155.0 mg, 0.53 mmol) and AIBN (10.3 mg, 0.06 mmol) in toluene (2 mL) was heated at 80°C for 30 min. The reaction mixture was subjected flash chromatography (silica gel/hexane–ethyl acetate 10:1 v/v then 3:1 v/v) to give **3a** in 85% yield (75.5 mg). Colorless oil. $[\alpha]_D=-13.1°$ (*c* 0.73, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 4.29 (quint, 1H, *J*=6.7 Hz), 4.03 (qd, 1H, *J*=6.1 Hz, 7.6 Hz), 3.68 (s, 3H), 2.78 (td, 1H, *J*=7.0, 10.1 Hz), 2.65 (dd, 1H, *J*=6.5, 15.6 Hz), 2.50 (dd, 1H, *J*=6.4, 15.4 Hz), 2.32 (td, 1H, *J*=6.8, 12.5 Hz), 2.18 (s, 3H), 1.88 (ddd, 1H, *J*=7.3, 9.8, 12.5 Hz), 1.32 (d, 3H, *J*=6.1 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 207.8, 171.2, 77.3, 74.6, 58.5, 51.7, 40.4, 35.0, 29.9, 20.8. Anal. calcd for $C_{10}H_{16}O_4$: C, 59.95; H, 8.05%. Found: C, 59.50; H, 8.02. Exact mass determination: 200.1057 (calcd $C_{10}H_{16}O_4$: 200.1049).

3.2.1. 3-Propionyl-5-(methoxycalbonyl)methy-2-methyl-tetrahydrofuran (3b). $[\alpha]_D=-18.9°$ (*c* 0.93, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 4.27 (quint, 1H, *J*=7.0 Hz), 4.03 (qd, 1H, *J*=6.3, 7.4 Hz), 3.68 (s, 3H), 2.78 (td, 1H, *J*=7.0, 9.8 Hz), 2.63 (dd, 1H, *J*=6.7, 15.6 Hz), 2.42–2.56 (m, 3H), 2.30 (td, 1H, *J*=6.7, 12.8 Hz), 1.87 (ddd, 1H, *J*=7.3, 9.8, 12.5 Hz), 1.30 (d, 3H, *J*=6.1 Hz), 1.05 (t, 3H, *J*=7.3 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 210.8, 170.6, 77.0, 74.2, 56.9, 51.0, 39.9, 35.5, 34.9, 20.0, 7.0. Exact mass determination: 214.1183 (calcd $C_{11}H_{18}O_4$: 214.1205).

3.2.2. 3-Acetyl-2-isopropyl-5-(methoxycalbonyl)methyl-tetrahydrofuran (3c). $[\alpha]_D=-15.9°$ (*c* 0.85, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 4.28 (qd, 1H, *J*=8.2, 6.4 Hz), 3.88 (t, 1H, *J*=6.1 Hz), 3.68 (s, 3H), 2.94 (quint, 1H, *J*=5.5 Hz), 2.64 (dd, 1H, *J*=6.4, 15.3 Hz), 2.47 (dd, 1H, *J*=6.4, 15.0 Hz), 2.22–2.27 (m, 1H), 2.20 (s, 3H), 1.71–1.86 (m, 2H), 0.93 (d, 3H, *J*=6.7 Hz), 0.88 (d, 3H, *J*=6.7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 86.1, 74.8, 54.2, 51.7, 40.4, 35.8, 32.7, 28.8, 18.7, 18.3. Exact mass determination: 228.1321 (calcd $C_{12}H_{20}O_4$: 228.1362).

3.2.3. 3-Acetyl-2-butyl-5-(methoxycalbonyl)methyl-tetrahydrofuran (3d). $[\alpha]_D=-24.3°$ (*c* 1.07, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 4.28 (quint, 1H, *J*=7.1 Hz), 3.99 (q, 1H, *J*=6.4 Hz), 3.68 (s, 3H), 2.85 (td, 1H, *J*=6.4, 9.8 Hz), 2.65 (dd, 1H, *J*=6.4, 15.3 Hz), 2.48 (dd, 1H, *J*=6.7, 15.6 Hz), 2.26 (m, 1H, *J*=6.4 Hz), 2.19 (s, 3H), 1.85 (ddd, 1H, *J*=7.9, 10.1, 12.8 Hz), 1.50–1.64 (m, 2H), 1.25–1.44 (m, 2H), 0.89 (t, 3H, *J*=6.7 Hz). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 81.4, 77.3, 74.9, 57.0, 51.7, 40.6, 35.5, 35.3, 28.2, 22.8, 14.0. Exact mass determination: 242.1537 (calcd $C_{13}H_{22}O_4$: 242.1518).

3.2.4. 3-Acetyl-5-(methoxycalbonyl)methy-2-phenyl-tetrahydrofuran (3e). $[\alpha]_D=-23.8$ (*c* 1.43, $CHCl_3$). ^1H NMR (250 MHz, $CDCl_3$) δ 7.26–7.38 (m, 5H), 4.97 (d, 1H, *J*=7.9 Hz), 4.49 (quint, 1H, *J*=6.7 Hz), 3.72 (s, 3H), 3.18 (td, 1H, *J*=7.3, 9.5 Hz), 2.80 (dd, 1H, *J*=6.4, 15.6 Hz), 2.65 (dd, 1H, *J*=6.4, 15.3 Hz), 2.45 (td, 1H, *J*=6.7, 12.8 Hz), 2.08 (s, 3H), 2.00–2.13 (m, 1H). ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 206.8, 170.6, 143.7, 128.1, 127.6, 125.7, 82.7, 74.8, 59.4, 51.2, 39.8, 34.8, 29.3. Anal. calcd for $C_{15}H_{18}O_4$: C, 68.69; H, 6.92%. Found: C, 68.78; H, 6.60. Exact mass determination: 262.1174 (calcd $C_{15}H_{18}O_4$: 262.1205).

3.2.5. 3-*tert*-Butoxycalbonyl-5-(methoxycalbonyl)methy-2-phenyl-tetrahydrofuran (3f). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.28–7.37 (m, 5H), 5.00 (d, 1H, J= 7.6 Hz), 4.54 (quint, 1H, J=6.9 Hz), 3.72 (s, 3H), 2.89 (ddd, 1H, J=6.3, 7.6, 13.5 Hz), 2.80 (dd, 1H, J=6.9, 15.2 Hz), 2.64 (dd, 1H, J=6.3, 15.5 Hz), 2.49 (quint, 1H, J=6.6 Hz), 2.00 (ddd, 1H, J=7.6, 9.6, 12.9 Hz), 1.43 (s, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 172.1, 171.1, 140.9, 128.9, 127.6, 125.8, 83.7, 75.2, 53.0, 51.6, 40.1, 35.5, 27.9, 27.3. Anal. calcd for $C_{18}H_{24}O_5$: C, 67.48; H, 7.55%. Found C, 67.24; H, 7.79.

3.2.6. 3-*tert*-Butoxycalbonyl-2-(4-chlorophenyl)-5-(methoxycalbonyl)methy-tetrahydrofuran (3g). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14–7.29 (m, 5H), 4.95 (d, 1H, J= 7.5 Hz), 4.53 (t, 1H, J=6.6 Hz), 3.71 (s, 3H), 2.75 (m, 2H), 2.47 (q, 1H, J=6.6 Hz), 2.04 (t, 1H, J=9.6 Hz), 1.96 (t, 1H, J=9.9 Hz), 1.43 (s, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.9, 171.1, 139.4, 133.3, 128.4, 127.3, 83.0, 81.3, 75.3, 52.9, 51.7, 40.0, 35.4, 27.9. Exact mass determination: 354.1192 (calcd $C_{18}H_{23}ClO_5$: 354.1234).

3.2.7. 3-*tert*-Butoxycalbonyl-5-(methoxycalbonyl)methy-3-methyl-2-phenyl-tetrahydrofuran (3h). ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14–7.29 (m, 5H), 5.23 (s, 1H), 4.14–4.48 (m, 1H), 3.72 (s, 3H), 2.67–2.87 (m, 5H), 1.51 (s, 9H), 1.01 (s, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 175.1, 171.4, 138.4, 127.9, 127.5, 126.5, 85.8, 81.2, 73.9, 53.8, 51.9, 44.8, 40.5, 28.1, 13.7. Exact mass determination: 334.1766 (calcd $C_{19}H_{26}O_5$: 334.1780).

3.3. Preparation of O-alkenylated precursors of tetrasubstituted tetrahydrofurans. Preparation of methyl 3-(2-*tert*-Butoxycarbonyl-1-phenyl-3-phenylselanylbutoxy)acrylate (4). General procedure

A mixture of *tert*-buty 2-(hydroxyphenylmethyl)-3-phenylselanylbutyrate (0.8062 g, 2.00 mmol), methyl propiolate (0.673 g, 8.00 mmol) and Et_3N (0.28 g, 2.00 mmol) in CH_2Cl_2 (20 mL) was allowed to stand at room temperature for 6 h. The reaction mixture was poured into HCl (1 M, 10 mL) and the resulting biphasic solution was extracted with CH_2Cl_2 (3×30 mL). Combined organic phase was dried over Na_2SO_4. After filtration and concentration, the crude product was purified through flash chromatography (hexane–ether 10:1) and **4-A** was isolated in 86% yield (0.8672 g, 1.77 mmol).

^{1}H NMR (270 MHz, $CDCl_3$) δ 7.24–7.46 (m, 10H), 7.46 (d, 1H, J=12.2 Hz), 5.43 (d, 1H, J=10.1 Hz), 5.25 (d, 1H, J= 12.5 Hz), 3.59–3.68 (m, 1H), 3.63 (s, 3H), 3.00 (dd, 1H, J=4.0, 9.9 Hz), 1.60 (d, 3H, J=7.2 Hz), 1.20 (s, 9H). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.8, 167.8, 161.0, 137.3, 134.8, 130.7, 129.0, 128.6, 127.9, 127.6, 98.9, 83.8, 82.1, 59.3, 51.1, 40.5, 27.7, 22.5. Exact mass determination: 490.1241 (calcd $C_{25}H_{30}O_5Se$: 490.1259).

4-C: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.48–8.08 (m, 11H), 5.45 (d, 1H, J=10.2 Hz), 5.27 (d, 1H, J=12.5 Hz), 3.63 (s, 3H), 2.94 (dd, 1H, J=4.0, 9.0 Hz), 2.70 (dq, 1H, J=4.0, 6.9 Hz), 1.53 (s, 3H), 1.43 (d, 3H, J=6.9 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 169.3, 167.9, 161.1, 136.7, 133.9, 129.3, 128.9, 128.8, 127.5, 127.4, 98.5, 84.9, 82.4, 59.0, 51.0, 37.9, 28.1, 27.6, 22.5. Exact mass determination: 490.1238 (calcd $C_{25}H_{30}O_5Se$: 490.1259).

4-D: ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.14–7.39 (m, 11H), 5.22 (d, 1H, J=8.6 Hz), 5.17 (d, 1H, J=12.5 Hz), 3.61 (s, 3H), 3.07 (dq, 1H, J=5.3, 6.9 Hz), 2.99 (dd, 1H, J=5.3, 8.9 Hz), 1.45 (s, 3H), 1.42 (d, 3H, J=9.6 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 168.8, 167.8, 161.0, 137.2, 134.7, 129.9, 129.0, 128.6, 127.8, 98.9, 83.8, 82.0, 59.4, 51.0, 40.5, 28.1, 27.7, 22.4.

3.3.1. 3-*tert*-Butoxycalbonyl-5-(methoxycalbonyl)methy-4-methyl-2-phenyl-tetrahydrofuran (5a). A mixture of **4-A** (0.1134 g, 0.23 mmol), Bu_3SnH (0.080 g, 0.28 mmol) and AIBN (0.016 g) in toluene (5 mL) was heated at 50°C and irradiated with sunlamp for 20 h. The reaction mixture was subjected to flash chromatography (hexane then hexane–ethyl acetate 10:1–3:1) to give **5a** in 98% yield (0.0754 g, 0.225 mmol). Anal. calcd for $C_{19}H_{26}O_5$: C, 68.24; H, 7.84. Found: C, 67.83; H, 7.98. ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.19–7.27 (m, 5H), 4.93 (d, 1H, J= 8.6 Hz), 4.55 (dd, 1H, J=8.9, 13.9 Hz), 3.65 (s, 3H), 2.72 (dd, 1H, J=7.3, 14.2 Hz), 2.52 (m, 2H), 2.40 (dd, 1H, J= 7.6, 8.7 Hz), 1.36 (s, 9H), 0.95 (d, 3H, J=7.3 Hz). ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.8, 171.6, 141.0, 127.8, 127.6, 125.8, 82.9, 81.3, 60.8, 57.2, 51.8, 41.2, 36.7, 28.1, 14.3. Exact mass determination: 334.1761 (calcd $C_{19}H_{26}O_5$: 334.1780).

Compound **5b** was prepared from **4-C** and **4-D** in a similar manner. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20–7.28 (m, 5H), 5.19 (d, 1H, J=9.3 Hz), 4.00 (td, 1H, J=5.9, 9.0 Hz), 3.71 (s, 3H), 2.99 (t, 1H, J=9.0 Hz), 2.78 (d, 2H, J=6.2 Hz), 2.44 (qt, 1H, J=6.7, 8.9 Hz), 1.10 (d, 3H, J=6.7 Hz), 1.00 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.7, 170.1, 139.0, 127.8, 127.7, 127.3, 81.4, 81.0, 80.5, 58.6, 51.7, 41.7, 38.4, 27.4, 15.7. Exact mass determination: 334.1800 (calcd $C_{19}H_{26}O_5$: 334.1780).

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