Intramolecular [2+2] Cycloaddition of Homoallylketenes to Bicyclo[2.1.1]hexan-5-ones

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Intramolecular [2+2] cycloaddition of *γ,δ*-unsaturated ketenes derived from hex-5-enoyl chloride derivatives gave bicyclo[2.1.1]hexan-5-ones with complete regioselectivity.

Key words intramolecular [2+2] cycloaddition; ketene; alkene; bicyclo[2.1.1]hexan-5-one; regioselective

Intramolecular [2+2] cycloaddition of ketenes to olefins is a powerful tool for stereo- and regioselective construction of polycyclic cyclobutanones.[1)] It is known that the tether length between ketenes and alkenes influences the yield of the intramolecular cycloaddition, and many examples of three-atom tethers have been reported.[1–4)] Intramolecular cycloaddition reactions of alkenylketenes with a longer tether have been achieved with reactive ketenes (keteniminium salts[5)] and alkoxyketenes[6)]) or ketenes having conformationally restricted tethers.[7)] On the other hand, reactions of alkenylketenes with a tether of less than three atoms are very rare. An allylketene **2**, which had a one-atom tether did not give a [2+2] adduct but gave cyclopentenone **3** in 79% yield (Chart 1).[8,9)] To the best of our knowledge, successful [2+2] cycloaddition of two-atom tethered homoallylketenes has not been reported to date except chromium–ketene complex.[10)] We want to report here intramolecular [2+2] cycloaddition of homoallylketenes free from chromium complexation.

Results and Discussion

We first investigated the reaction of homoallylketene **5**, and it was found that bicyclo[2.1.1]hexan-5-one **7** was isolated in 71% yield by treatment of carboxylic acid chloride **4** with diisopropylethylamine in acetonitrile at reflux (Chart 2).[9)] The bicyclo[2.1.1]hexan-5-one structure of **7** was unambiguously determined by X-ray crystallographic analysis.[11)] The other regioisomer **6** was not obtained at all. This result showed a cycloaddition regioselectivity opposite to that was expected by electronic consideration.[12,13)] Thus, intramolecular [2+2] cycloaddition of ketene with a longer-tethered terminal alkene usually gives a fused compound **9** rather than a bridged compound **10** since the more nucleophilic terminal alkenyl carbon attacks the electrophilic ketene carbon (Chart 3). In fact, intramolecular cycloaddition of a three-carbon-tethered ketene **12** afforded **13** as the major product with normal regioselectivity (Chart 4).[9,14)]

Effects of substituents on ketenes derived from carboxylic acid chlorides **15a–j** were studied to clarify the scope and limitations of the present intramolecular [2+2] cycloaddition of homoallylketenes (Table 1). The carboxylic acid chlorides **15a–j** were prepared from the corresponding carboxylic acids by using oxalyl chloride in dichloromethane. After evaporation of volatiles, a carboxylic acid chloride was dissolved in acetonitrile and diisopropylethylamine was added. The resulting reaction mixture was stirred at reflux for 11 h. A monosubstituted ketene formed from hex-5-enoyl chloride **15a** did not give the desired product **16a** because dimerization or oligomerization of the ketene proceeded faster (entry 1). Similar low efficiency of a monoalkylketene was reported in

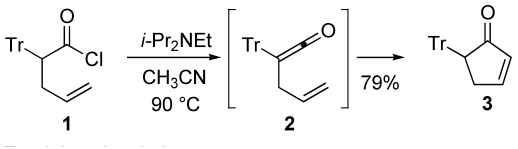
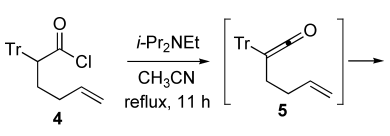


Chart 1



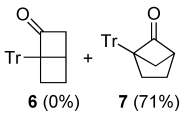


Chart 2

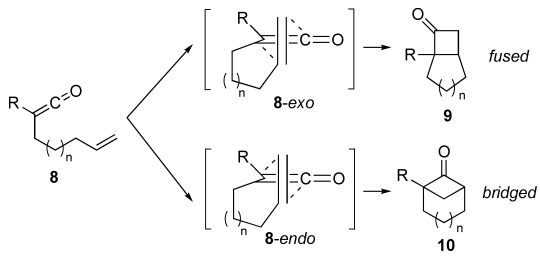
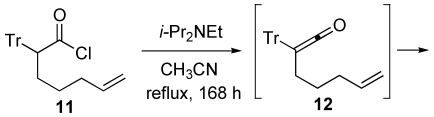


Chart 3. Intramolecular [2+2] Cycloaddition of a Ketene with a Terminal Alkene



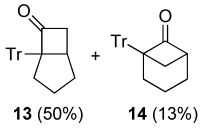


Chart 4

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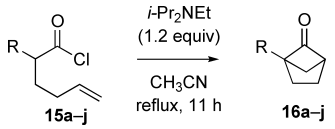
Table 1. Intramolecular [2+2] Cycloaddition of Homoallylketenes to Bicyclo[2.1.1]hexan-5-ones **16a–j**



Entry	**15**	R	**16**	Yield (%)[a)]
1	**15a**	H	**16a**	0
2	**15b**	Bu	**16b**	63
3	**15c**	Bn	**16c**	69
4	**15d**	1-Naphthylmethyl	**16d**	40
5	**15e**	Cy	**16e**	79
6	**15f**	*t*-Bu	**16f**	67
7	**15g**	Ph	**16g**	70
8	**15h**	MeO	**16h**	0
9	**15i**	BnO	**16i**	20
10	**15j**	PhS	**16j**	31

a) Isolated yield.[9)]

three-carbon-tethered ketenes.[14)] Intramolecular cycloaddition of alkylhomoallylketenes gave the corresponding cycloadducts **16b–f** in moderate to good yields (entries 2–6). Cycloaddition of a phenylketene derived from **15g** also proceeded to afford an adduct **16g** in 70% yield (entry 7). However, intramolecular cycloaddition of alkoxyketenes generated from **15h**, **i** did not proceed smoothly (entries 8 and 9). These results were in contrast with the efficient [2+2] cycloaddition of alkoxyketene derived from chromium–carbene complex.[10)] It is assumed that problematic generation of ketenes from **15h**, **i** under the basic conditions would cause the low conversion to **16h**, **i**. An α-phenylsulfany derivative **15j** gave the corresponding bicyclo[2.1.1]hexan-5-one **16j** in 31% yield (entry 10). In all of the experiments described above, a small amount of the corresponding carboxylic acid anhydrides was formed,[15)] but the other regioisomers, [2.2.0]hexan-2-ones, were not obtained.

The unusual regioselectivity observed in cycloaddition of homoallylketene **8** (n=0) was explained by high ring strain of fused [2.2.0]hexan-2-one **9** (n=0).[16)] Even if [2.2.0]hexan-2-one **9** (n=0) was formed, reversibility of ketene cycloaddition[1)] would lead to the more stable bridged regioisomer **10** (n=0).

In summary, intramolecular [2+2] cycloaddition of homoallylketenes derived from hex-5-enoyl chlorides with diisopropylethylamine gave bicyclo[2.1.1]hexan-5-ones.[17,18)] These compounds have been prepared by photolysis of γ,δ-unsaturated chromium–carbene complexes,[10)] intramolecular alkylation of 2-tosyloxymethylcyclopentanones[19,20)] and β'-silyloxy enol triflate,[21)] or oxidative rearrangement of bicyclo[2.2.0]hexan-2-ol.[22)] The present method would offer an another useful method for synthesis of bicyclo[2.1.1]hexan-5-ones.[23)]

Experimental

General All melting points were determined on Yanagimoto micro melting point apparatus and are uncorrected. Infrared spectra (IR) were recorded on Horiba IR-710. ^{1}H-NMR spectra were recorded on a JOEL JNM ECA600 (600 MHz) or a JOEL JNM ECS400 (400 MHz) spectrometer at room temperature; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting pattern are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. ^{13}C-NMR spectra were recorded on a JOEL JNM ECA600 (150 MHz) or a JOEL JNM ECS400 (100 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in parts per million relative to tetramethylsilane with the solvent resonance as the internal standard $CDCl_3$. Analytical TLC was performed on Merck precoated TLC plates (silica gel 60 GF254, 0.25 mm). Silica-gel column chromatography was carried out on silica gel 60 N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. All reactions were carried out under nitrogen in dried glassware with magnetic stirring. Diisopropylamine was used after distillation from CaH_2.

Preparation of Substrates for Intramolecular [2+2] Cycloaddition. 2-Tritylhex-5-enoic Acid (a Substrate of 4) To a stirred solution of sodium hydride (60% oil suspension, 71.2 mg, 1.78 mmol) in tetrahydrofuran (THF) (8 mL) was added 3,3,3-triphenylpropionic acid (500.0 mg, 1.65 mmol), and the mixture was refluxed for 15 min and the mixture was cooled to 0°C. *n*-Butyllithium (1.65 M in hexane, 1.20 mL, 1.98 mmol) was added and the mixture was stirred for 5 min. 4-Bromo-1-butene (0.201 mL, 1.98 mmol) was added and the mixture was stirred at 30°C for 23 h. The reaction mixture was quenched with 5% hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (25 g, hexane–ethyl acetate=3 : 1) to afford 2-tritylhex-5-enoic acid (85.2 mg, 0.239 mmol, 14%) as a colorless crystal: mp 138.0–139.0°C (hexane, ethyl acetate); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.31–1.37 (m, 1H), 1.69 (dt, J=14.4, 8.2 Hz, 1H), 2.04–2.17 (m, 2H), 4.21 (d, J=11.0 Hz, 1H), 5.01–5.05 (m, 2H), 5.78 (ddt, J=17.2, 10.3, 7.6 Hz, 1H), 7.14–7.17 (m, 3H), 7.19–7.22 (m, 6H), 7.30–7.31 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 29.9, 32.1, 50.9, 60.1, 116.0, 126.1, 126.1, 127.4, 129.9, 137.2, 145.0, 180.1; IR ($CHCl_3$) cm^{-1}: 1709, 1495, 1446, 706; *Anal.* Calcd for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 84.27; H, 6.78.

2-Tritylhept-6-enoic Acid (a Substrate of 11) To a stirred solution of sodium hydride (60% oil suspension, 65.8 mg, 1.65 mmol) in THF (8 mL) was added 3,3,3-triphen-

ylpropionic acid (499.9 mg, 1.65 mmol), and the mixture was refluxed for 15 min and the mixture was cooled to 0°C. *n*-Butyllithium (1.65 M in hexane, 1.17 mL, 1.93 mmol) was added and the mixture was stirred for 5 min. 5-Bromo-1-pentene (0.23 mL, 1.94 mmol) was added and the mixture was stirred at 30°C for 23 h. The reaction mixture was quenched with 5% hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (13 g, hexane–ethyl acetate=7 : 1) to afford 2-tritylhept-6-enoic acid (273.7 mg, 0.739 mmol, 45%) as a colorless crystal: mp 142.0–143.5°C (hexane, ethyl acetate); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.19–1.25 (m, 1H), 1.41–1.49 (m, 2H), 1.59–1.65 (m, 1H), 1.96–2.02 (m, 2H), 4.12–4.15 (m, 1H), 4.91 (dd, J=10.3, 1.0 Hz, 1H), 4.95 (dq, J=17.2, 2.1 Hz, 1H), 5.68–5.76 (m, 1H), 7.12–7.14 (m, 3H), 7.17–7.19 (m, 6H), 7.27–7.29 (m, 6H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 27.5, 30.4, 33.5, 52.0, 60.2, 114.7, 126.1, 127.4, 129.9, 138.2, 145.1, 180.2; IR ($CHCl_3$) cm^{-1}: 1708, 1495, 1446, 706; *Anal.* Calcd for $C_{26}H_{26}O_2$: C, 84.29; H, 7.07. Found: C, 84.29; H, 7.20.

2-Butylhex-5-enoic Acid (a Substrate of 15b) To a stirred solution of sodium hydride (60% oil suspension, 89.6 mg, 2.24 mmol) in THF (18 mL) was added 5-hexenoic acid (253.5 mg, 2.22 mmol), and the mixture was refluxed for 10 min and then cooled to 0°C. A solution of lithium diisopropylamide which was prepared by adding *n*-butyllithium (1.67 M in hexane, 1.33 mL, 2.22 mmol) to a solution of diisopropylamine (0.373 mL, 2.66 mmol) in THF (8 mL) was cannulated and the mixture was stirred few minutes. 4-Bromo-1-butane (0.24 mL, 2.24 mmol) was added, and the resulting cake was heated at 30°C for 63 h. The reaction mixture was quenched with 5% hydrochloric acid at room temperature, and the mixture was extracted with ether. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (6 g, hexane–ether=3 : 1) to afford 2-butylhex-5-enoic acid (134.3 mg, 0.789 mmol, 36%) as a pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.90 (t, J=6.9 Hz, 3H), 1.27–1.35 (m, 4H), 1.46–1.52 (m, 1H), 1.54–1.59 (m, 1H), 1.61–1.67 (m, 1H), 1.72–1.78 (m, 1H), 2.04–2.15 (m, 2H), 2.38 (tt, J=8.9, 5.5 Hz, 1H), 4.97 (dd, J=10.0, 1.4 Hz, 1H), 5.03 (dq, J=17.2, 1.7 Hz, 1H), 5.79 (ddt, J=17.2, 10.3, 6.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.9, 22.6, 29.4, 31.2, 31.5, 31.8, 44.9, 115.1, 137.8, 182.7; IR ($CHCl_3$) cm^{-1}: 1705, 918; high resolution (HR)-MS (EI+) Calcd for $C_{10}H_{18}O_2$ (*m*/*z*) 170.1307, Found 170.1304.

2-Benzylhex-5-enoic Acid[24] **(a Substrate of 15c)** To a stirred solution of diisopropylamine (0.614 mL, 4.38 mmol) in THF (20 mL) was added dropwise at 0°C *n*-butyllithium (1.67 M in hexane, 2.62 mL, 4.38 mmol), and the mixture was stirred at 0°C for 15 min. 5-Hexenoic acid (201.1 mg, 1.76 mmol) was added and the mixture was stirred for 15 min. Benzyl bromide (0.25 mL, 2.10 mmol) was added and the mixture was stirred at room temperature for 15 h. The reaction mixture was quenched with 5% hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative thin-layer chromatography on silica gel (hexane–ether=2:1) to afford 2-benzylhex-5-enoic acid (293.1 mg, 1.43 mmol, 81%) as a colorless oil.

2-[(Naphthalen-1-yl)methyl]hex-5-enoic Acid (a Substrate of 15d) To a stirred solution of diisopropylamine (4.59 mL, 32.8 mmol) in THF (100 mL) was added dropwise at 0°C *n*-butyllithium (1.62 M in hexane, 20.2 mL, 32.7 mmol), and the mixture was stirred at 0°C for 15 min. 5-Hexenoic acid (1.50 g, 13.1 mmol) was added and the mixture was stirred for 20 min. 1-(Chloromethyl)naphthalene (2.35 mL, 15.7 mmol) was added and the mixture was stirred at room temperature for 22 h. The reaction mixture was quenched with 1 N hydrochloric acid and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (40 g, hexane–ethyl acetate=4 : 1), and then purified by recrystallization from hexane and dichloromethane to afford 2-[(naphthalen-1-yl) methyl]hex-5-enoic acid (1.47 g, 5.78 mmol, 44%) as a colorless crystal: mp 75.5–76.0°C (hexane, dichloromethane); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.64–1.69 (m, 1H), 1.86 (ddt, J=14.8, 9.3, 5.5 Hz, 1H), 2.03–2.09 (m, 1H), 2.14–2.20 (m, 1H), 2.90 (ddt, J=9.3, 7.6, 4.8 Hz, 1H), 3.19 (dd, J=14.1, 7.2 Hz, 1H), 3.49 (dd, J=14.1, 7.2 Hz, 1H), 4.94 (dd, J=10.3, 1.4 Hz, 1H), 4.99 (dq, J=17.2, 1.7 Hz, 1H), 5.73 (ddt, J=16.8, 10.0, 6.5 Hz, 1H), 7.32–7.34 (m, 1H), 7.36–7.39 (m, 1H), 7.47–7.49 (m, 1H), 7.51–7.54 (m, 1H), 7.74 (d, J=7.9 Hz, 1H), 7.86 (d, J=7.2 Hz, 1H), 8.02 (d, J=8.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 31.1, 31.4, 35.4, 45.8, 115.4, 123.5, 125.4, 125.6, 126.1, 127.2, 127.4, 128.9, 131.8, 133.9, 134.8, 137.5, 181.8; IR ($CHCl_3$) cm^{-1}: 1709, 1703, 918, 798; *Anal.* Calcd for $C_{17}H_{18}O_2$: C, 80.28; H, 7.13. Found: C, 80.11; H, 7.05.

2-Cyclohexylhex-5-enoic Acid (a Substrate of 15e) To a stirred solution of sodium hydride (60% oil suspension, 574.8 mg, 14.4 mmol) in THF (30 mL) was added cyclohexaneacetic acid (2.00 g, 14.1 mmol), and the mixture was refluxed for 10 min and then cooled to 0°C. A solution of lithium diisopropylamide which was prepared by adding *n*-butyllithium (1.67 M in hexane, 10.1 mL, 16.9 mmol) to a solution of diisopropylamine (2.40 mL, 17.1 mmol) in THF (15 mL) was cannulated and the mixture was stirred few minutes. 4-Bromo-1-butene (1.40 mL, 13.8 mmol) was added, and the resulting cake was heated at 30°C for 5 h. The reaction mixture was quenched with 5% hydrochloric acid at room temperature, and the mixture was extracted with ether. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (20 g, hexane–ether=7 : 1) to afford 2-cyclohexylhex-5-enoic acid (979.1 mg, 4.89 mmol, 35%) as a pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.00 (dq, J=12.4, 3.1 Hz, 1H), 1.06–1.18 (m, 2H), 1.20–1.28 (m, 2H), 1.53–1.75 (m, 7H), 1.79–1.81 (m, 1H), 1,98–2.04 (m, 1H), 2.09–2.16 (m, 1H), 2.20 (ddd, J=11.0, 7.6–4.1 Hz, 1H), 4.97 (ddt, J=10.3, 1.4, 1.4 Hz, 1H), 5.03 (dq, J=17.2, 1.7 Hz, 1H), 5.79 (ddt, J=17.2, 10.3, 6.9 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 26.3, 26.3, 28.2, 30.4, 30.9, 31.9, 40.0, 51.2, 115.1, 137.9, 182.0; IR ($CHCl_3$) cm^{-1}: 1703, 1641, 1450, 910; HR-MS (EI+) Calcd for $C_{12}H_{14}O_2S$ (*m*/*z*) 196.1463, Found 196.1469.

2-*tert*-Butylhex-5-enoic Acid (a Substrate of 15f) To a stirred solution of sodium hydride (60% oil suspension, 695.6 mg, 17.4 mmol) in THF (45 mL) was added 3,3-dimethylbutyric acid (2.00 g, 17.2 mmol), and the mixture was refluxed

for 15 min and the mixture was cooled to 0°C. *n*-Butyllithium (1.65 M in hexane, 12.5 mL, 20.6 mmol) was added and the mixture was stirred for 5 min. 4-Bromo-1-butene (2.10 mL, 20.7 mmol) was added and the mixture was stirred at 30°C for 2 h. The reaction mixture was quenched with 5% hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by Kugelrohr distillation (100°C/10.5 mmHg) and the distillation residue was purified by column chromatography on silica gel (5 g, hexane–ether=6 : 1) to afford 2-*tert*-butylhex-5-enoic acid (168.4 mg, 0.989 mmol, 6%) as a yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.10 (s, 9H), 1.54–1.60 (m, 1H), 1.73–1.80 (m, 1H), 1.95–2.01 (m, 1H), 2.10–2.16 (m, 1H), 2.18 (dd, J=12.0, 2.4 Hz, 1H), 4.98 (dd, J=10.3, 1.4 Hz, 1H), 5.04 (dq, J=17.2, 1.7 Hz, 1H), 5.79 (ddt, J=17.2, 10.3, 7.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 26.8, 27.8, 32.5, 32.7, 55.6, 115.3, 137.8, 181.5; IR ($CHCl_3$) cm^{-1}: 1703, 1369, 918; HR-MS (EI+) Calcd for $C_{10}H_{18}O_2$ (*m*/*z*) 170.1307, Found 170.1308.

2-Phenylhex-5-enoic Acid (a Substrate of 15g) To a stirred mixture of potassium hydride (1.66 g, 29.6 mmol) in dimethyl sulfoxide (DMSO) (25 mL) was added at 0°C trifluoromethanesulfonic acid (1.12 mL, 12.7 mmol), and the resulting mixture was stirred at room temperature for 15 min. 4-Bromo-1-butene (1.03 mL, 10.1 mmol) and diethyl phenylmalonate (2.00 g, 8.47 mmol) were added successively at room temperature, and the reaction mixture was stirred at 50°C for 12 h. The reaction mixture was quenched with 1 N hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (30 g, hexane–ether=8 : 1) to afford diethyl 2-(butyl-3-enyl)-2-phenylmalonate (2.07 g, 7.11 mmol, 84%) as a colorless oil.

To a stirred solution of diethyl 2-(butyl-3-enyl)-2-phenylmalonate (2.06 g, 7.09 mmol) in ethanol (13 mL) was added a solution of potassium hydroxide (1.19 g, 21.2 mmol) in water (8 mL), and the mixture was refluxed for 6 h. After evaporation of the solvent, the residue was extracted with 10% aqueous solution of potassium hydroxide. The water extracts were acidified to pH 2 with 10% hydrochloric acid, and the mixture were extracted with ether. The combined organic extracts was washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The obtained 2-(but-3-enyl)-2-phenylmalonic acid was heated at 155°C for 14 h. The crude product was purified by column chromatography on silica gel (13 g, hexane–ethyl acetate=2 : 1) to afford 2-phenylhex-5-enoic acid (984.9 mg, 5.18 mmol, 73% for 2 steps) as a pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.86 (ddt, J=14.8, 7.6, 7.6 Hz, 1H), 2.00 (q, J=6.9 Hz, 2H), 2.15 (ddt, J=14.3, 7.6 Hz, 1H), 3.56 (t, J=7.2 Hz, 1H), 4.97–5.01 (m, 2H), 5.75 (ddt, J=16.5, 10.3, 6.2 Hz, 1H), 7.26–7.28 (m, 1H), 7.30–7.32 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 31.3, 32.0, 50.8, 115.5, 127.4, 128.1, 128.6, 137.3, 138.2, 180.5; IR ($CHCl_3$) cm^{-1}: 1709, 918, 700; HR-MS (EI+) Calcd for $C_{12}H_{14}O_2$ (*m*/*z*) 190.0994, Found 190.0992.

2-(Benzyloxy)hex-5-enoic Acid[25] (a Substrate of 15i) To a dry flask containing magnesium (2.52 g, 103.7 mmol) was added a solution of the 4-bromo-1-butene (4.51 mL, 44.4 mmol) in THF (60 mL) dropwise with vigorous agitation. The resultant solution was then added dropwise to a mixture of diethyl oxalate (5.0 mL, 37.1 mmol), THF (45 mL) and diethyl ether (60 mL) at −78°C and the solution stirred for 4 h, then stirred for 9 h at room temperature. The reaction was quenched with saturated ammonium chloride solution and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (80 g, hexane–ether=11 : 1) to afford ethyl 2-oxohex-5-enoate (5.45 g, 34.7 mmol, 94%) as a pale yellow oil.

Sodium triacetoxyborohydride (6.29 g, 39.3 mmol) was added to a solution of ethyl 2-oxohex-5-enoate (5.45 g, 34.7 mmol) in dichloromethane (150 mL). The mixture was stirred at room temperature for 1 d. Then, sodium triacetoxyborohydride (5.72 g, 35.7 mmol) was added to the mixture. The mixture was stirred at room temperature for 2 d. The solution was quenched with saturated aqueous sodium hydrogen carbonate solution and the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (60 g, hexane–diethyl ether=11 : 1) to afford ethyl 2-hydroxyhex-5-enoate (3.53 g, 22.2 mmol, 64%) as a colorless oil.

Silver(I) oxide (1.91 g, 8.25 mmol), benzyl bromide (1.0 mL, 5.85 mL) and tetrabutylammonium iodine (2.03 g, 5.50 mmol) were added to a *N*,*N*-dimethylformamide (DMF) (25 mL) solution of ethyl 2-hydroxyhex-5-enoate (874.8 mg, 5.50 mmol), the resulting mixture was stirred for 8 h at room temperature. The reaction mixture was filtered and extracted with diethyl ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (15 g, hexane–diethyl ether=10 : 1) to afford ethyl 2-(benzyloxy)hex-5-enoate (737.5 mg, 2.97 mmol, 54%) as a pale yellow oil.

To a stirred solution of ethyl 2-(benzyloxy)hex-5-enoate (344.5 mg, 1.39 mmol) in ethanol (8 mL) was added a solution of potassium hydroxide (235.5 mg, 4.20 mmol) in water (6 mL), and the mixture was refluxed for 13 h. After evaporation of the solvent, the residue was acidified to pH 2 with 5% hydrochloric acid, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford 2-(benzyloxy)hex-5-enoic acid (270.4 mg, 1.23 mmol, 88%) as a pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.92 (dt, J=7.6, 6.2 Hz, 2H), 2,17–2.28 (m, 2H), 4.02 (t, J=6.2 Hz, 1H), 4.48 (d, J=11.3 Hz, 1H), 4.73 (d, J=11.3 Hz, 1H), 4.98–5.04 (m, 2H), 5.78 (ddt, J=17.2, 10.3, 6.9 Hz, 1H), 7.30–7.34 (m, 1H), 7.35–7.37 (m, 4H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 29.2, 31.8, 72.6, 76.7, 115.7, 128.1, 128.1, 128.4, 137.0, 137.1, 178.3; IR ($CHCl_3$) cm^{-1}: 1720, 698; HR-MS (EI+) Calcd for $C_{13}H_{16}O_3$ (*m*/*z*) 220.1099, Found 220.1103.

2-(Phenylthio)hex-5-enoic Acid (a Substrate of 15j) To a stirred solution of diisopropylamine (2.10 mL, 15.0 mmol) in THF (30 mL) was added dropwise at 0°C *n*-butyllithium (1.67 M in hexane, 8.98 mL, 15.0 mmol), and the mixture was stirred at 0°C for 20 min. (Phenylthio)acetic acid (1.01g, 6.00 mmol) was added and the mixture was stirred for 20 min. 4-Bromo-1-butene (1.22 mL, 12.0 mmol) was added and the mixture was stirred at room temperature for 24 h. The reaction

mixture was quenched with 5% hydrochloric acid and extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (25 g, hexane–ethyl acetate=2 : 1) to afford 2-(phenylthio)hex-5-enoic acid (1.22 g, 5.53 mmol, 92%) as a yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.86 (ddt, J=14.4, 7.2, 7.2 Hz, 1H), 2.00 (ddt, J=15.1, 7.6, 7.6 Hz, 1H), 2.25 (q, J=7.2 Hz, 2H), 3.64 (t, J=7.6 Hz, 1H), 5.02 (dd, J=10.3, 1.4 Hz, 1H), 5.06 (dq, J=17.2, 1.4 Hz, 1H) 5.77 (ddt, J=16.8, 10.3, 6.5 Hz, 1H), 7.29–7.33 (m, 3H), 7.47–7.49 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 30.4, 31.0, 49.9, 116.2, 128.2, 129.0, 132.8, 133.0, 136.5, 178.5; IR ($CHCl_3$) cm^{-1}: 1708, 919; HR-MS (EI+) Calcd for $C_{12}H_{14}O_2S$ (*m*/*z*) 222.0715, Found 222.0709.

Typical Procedure for Intramolecular [2+2] Cycloaddition: Preparation of 1-Tritylbicyclo[2.1.1]hexane-5-one (7) To a stirred solution of 2-tritylhex-5-enoic acid (32.7 mg, 0.0917 mmol) in dichloromethane (1.5 mL) was added at 0°C oxalyl chloride (0.023 mL, 0.272 mmol) and the mixture was stirred for 17 h. The volatiles were evaporated *in vacuo* to remove all of excess oxalyl chloride and dichloromethane. To the resulting acid chloride acetonitrile (0.46 mL) and *N*,*N*-diisopropylethylamine (0.0188 mL, 0.110 mmol) were added successively at room temperature, and the mixture was refluxed for 11 h. The reaction mixture was quenched with saturated aqueous sodium hydrogen carbonate solution at room temperature, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, filtered, and concentrated. The crude product was purified by preparative thin-layer chromatography on silica gel (hexane–ethyl acetate=10 : 1) to afford 1-tritylbicyclo[2.1.1]hexane-5-one **7** (22.0 mg, 0.0650 mmol, 71%) as a colorless crystal: mp 168.0–169.0°C (hexane, ethyl acetate); ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.27 (td, J=11.7, 4.5 Hz, 1H), 1.42 (d, J=7.6 Hz, 1H), 1.69 (tdd, J=11.7, 3.8, 1.7 Hz, 1H), 1.89–1.93 (m, 1H), 2.03–2.07 (m, 1H), 2.14 (dq, J=7.6, 2.7 Hz, 1H), 2.82 (dt, J=3.4, 1.7 Hz, 1H), 7.20–7.26, (m, 15H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.6, 26.9, 49.5, 60.1, 72.3, 126.1, 127.6, 130.3, 202.9; IR ($CHCl_3$) cm^{-1}: 1772, 706; *Anal*. Calcd for $C_{25}H_{22}O$: C, 88.72; H, 6.55. Found: C, 88.89; H, 6.64.

5-Tritylbicyclo[3.2.0]heptan-6-one (13) Colorless crystal: mp 184.0–186.0°C (hexane, ethyl acetate) ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.69–1.88 (m, 4H), 1.96–2.02 (m, 1H), 2.13 (dd, J=12.7, 6.9 Hz, 1H), 2.37–2.42 (m, 1H), 3.09–3.15 (m, 2H), 7.03–7.34 (m, 15H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 24.4, 33.1, 36.4, 38.7, 50.6, 62.7, 85.4, 126.3, 126.5, 127.2, 127.6, 127.8, 129.5, 130.5, 131.7, 144.7, 145.3, 147.1, 215.1; IR ($CHCl_3$) cm^{-1}: 1764, 704; HR-MS (EI+) Calcd for $C_{26}H_{24}O$ (*m*/*z*) 352.18272, Found 352.18242.

1-Butylbicyclo[2.1.1]hexan-5-one (16b) Pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 0.90 (t, J=7.2 Hz, 3H), 1.30–1.38 (m, 4H), 1.40 (d, J=7.2 Hz, 1H), 1.54 (dq, J=7.1, 2.7 Hz, 1H), 1.58–1.75 (m, 4H), 1.79 (tdd, J=11.0, 4.5, 1.7 Hz, 1H), 1.85–1.90 (m, 1H), 2.83 (dt, J=3.1, 1.7 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 13.9, 22.1, 23.2, 25.1, 26.8, 27.7, 31.2, 52.7, 65.9, 202.1; IR ($CHCl_3$) cm^{-1}: 1776, 1765; HR-MS (EI+) Calcd for $C_{10}H_{16}O$ (*m*/*z*) 152.12012, Found 152.11996.

1-Benzylbicyclo[2.1.1]hexan-5-one (16c) Colorless oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.35 (d, J=7.2 Hz, 1H), 1.56 (dq, J=7.2, 2.7 Hz, 1H), 1.60–1.67 (m, 2H), 1.71–1.76 (m, 1H) 1.83–1.88 (m, 1H), 2.83 (dt, J=3.1, 1.7 Hz, 1H), 2.93 (d, J=14.1 Hz, 1H) 3.02 (d, J=14.4 Hz, 1H), 7.20–7.30 (m, 5H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.9, 24.9, 31.3, 34.0, 52.2, 66.0, 126.1, 128.3, 129.4, 138.0, 201.2; IR ($CHCl_3$) cm^{-1}: 1786, 1770, 704; HR-MS (EI+) Calcd for $C_{13}H_{14}O$ (*m*/*z*) 186.10447, Found 186.10414.

1-[(Naphthalen-1-yl)methyl]bicyclo[2.1.1]hexan-5-one (16d) Pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.32 (d, J=7.6, 1H), 1.53 (dq, J=7.2, 2.4 Hz, 1H), 1.58–1.63 (m, 1H), 1.66–1.73 (m, 2H), 1.82–1.86 (m, 1H), 2.81–2.82 (m, 1H), 3.41 (d, J=14.8 Hz, 1H), 3.50 (d, J=14.4 Hz, 1H), 7.39–7.42 (m, 2H), 7.46–7.52 (m, 2H), 7.73 (dd, J=6.9, 2.4 Hz, 1H), 7.85 (dd, J=7.9, 0.7 Hz, 1H), 8.03 (d, J=8.2 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 22.0, 25.4, 29.8, 32.0, 52.4, 66.0, 124.0, 125.5, 125.7, 127.0, 127.7, 128.7,132.3, 133.8, 134.5, 201.2; IR ($CHCl_3$) cm^{-1}: 1776, 1018; HR-MS (DART) Calcd for $C_{17}H_{16}O$ (*m*/*z*) 236.12011, Found 236.12088.

1-Cyclohexylbicyclo[2.1.1]hexan-5-one (16e) Colorless oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.04–1.18 (m, 3H), 1.21–1.29 (m, 2H), 1.35 (d, J=7.2 Hz, 1H), 1.57–1.58 (m, 1H), 1.64–1.79 (m, 9H), 1.83–1.87 (m, 1H), 2.79–2.80 (m, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.7, 22.4, 26.2, 26.2, 26.3, 28.7, 29.2, 29.4, 36.2, 52.3, 69.7, 202.4; IR ($CHCl_3$) cm^{-1}: 2929, 1766, 1450; HR-MS (EI+) Calcd for $C_{12}H_{18}O$ (*m*/*z*) 178.13538, Found 178.13577.

1-*tert*-Butylbicyclo[2.1.1]hexan-5-one (16f) Pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.00 (s, 9H), 1.32 (d, J=7.2 Hz, 1H), 1.70 (dq, J=5.2, 2.4 Hz, 1H), 1.72–1.82 (m, 3H), 1.83–1.87 (m, 1H), 2.77 (dt, J=3.1, 1.7 Hz, 1H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.7, 21.8, 26.4, 28.2, 30.1, 51.9, 72.9, 202.2; IR ($CHCl_3$) cm^{-1}: 1776, 1769; HR-MS (EI+) Calcd for $C_{10}H_{16}O$ (*m*/*z*) 152.12012, Found 152.12036.

1-Phenylbicyclo[2.1.1]hexane-5-one (16g) Pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.84 (d, J=7.6 Hz, 1H), 1.97 (tdd, J =10.7, 5.5, 1.7 Hz, 1H), 2.01–2.06 (m, 2H), 2.10–2.18 (m, 2H), 3.03 (dt, J=3.1, 1.7 Hz, 1H), 7.25–7.37 (m, 5H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 22.1, 27.3, 32.8, 53.1, 67.9, 127.0, 127.2, 128.4, 136.0, 199.5; IR ($CHCl_3$) cm^{-1}: 1786, 1776, 1770, 700; HR-MS (EI+) Calcd for $C_{12}H_{12}O$ (*m*/*z*) 172.08882, Found 172.08859.

1-(Benzyloxy)bicyclo[2.1.1]hexan-5-one (16i) Pale yellow oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.60 (d, J=6.9 Hz, 1H), 1.78–1.96 (m, 5H), 2.58 (dt, J=2.8, 1.4 Hz, 1H), 4.68 (d, J=11.3 Hz, 1H), 4.88 (d, J=11.3 Hz, 1H), 7.29 (tt, J=6.5, 1.7 Hz, 1H), 7.33–7.38 (m, 4H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 21.7, 23.6, 30.2, 45.0, 69.4, 91.9, 127.6, 127.8, 128.4, 137.7, 200.2; IR ($CHCl_3$) cm^{-1}: 1793, 1321; HR-MS (EI+) Calcd for $C_{13}H_{14}O_2$ (*m*/*z*) 202.09938, Found 202.0988.

1-(Phenylthio)bicycle[2.1.1]hexan-5-one (16j) Colorless oil: ^{1}H-NMR (600 MHz, $CDCl_3$) δ: 1.61 (d, J=7.6 Hz, 1H), 1.76–1.78 (m, 1H), 1.83–1.96 (m, 4H), 2.89–2.90 (m, 1H), 7.30–7.31 (m, 3H), 7.57–7.59 (m, 2H); ^{13}C-NMR (150 MHz, $CDCl_3$) δ: 22.5, 26.6, 33.3, 50.7, 66.6, 128.3, 128.8, 131.2, 135.0, 197.8; IR ($CHCl_3$) cm^{-1}: 1795; HR-MS (EI+) Calcd for $C_{12}H_{12}SO$ (*m*/*z*) 204.06089, Found 204.06057.

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