Electronic Supplementary Information

Intramolecular formal [4 + 2] cycloaddition of 3-ethoxycyclobutanones and alkenes

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1. General

All melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100. ¹H NMR spectra were recorded on a JEOL JNM EX270 (270 MHz) or a JEOL JNM GSX500 (500 MHz) spectrometer; chemical shifts (δ) are reported in parts per million relative to tetramethylsilane. Splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. ¹³C NMR spectra were recorded on a JEOL JNM EX270 (270 MHz) or a JEOL JNM GSX500 (500 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 CDCl₃. High resolution mass spectra (HRMS) were recorded on a JEOL JMS-SX-102A mass spectrometer (EI). Elemental analyses were carried out on a Yanaco CHN Corder MT-5. 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 60N (Kanto Kagaku Co., Ltd., spherical, neutral, 63–210 μm). Preparative thin-layer chromatography (PTLC) was carried out on silica gel Wakogel B-5F. Dichloromethane was distilled under argon from calcium hydride before use. All cycloaddition reactions were carried out under argon in dried glassware with magnetic stirring. A solution of EtAlCl₂ in hexane (1.04 M) was purchased from Aldrich. The reaction conditions for the preparation of 3-ethoxycyclobutanones were not optimized.

2. Typical experimental procedures and characterization data

2.1 Boron trifluoride etherate-catalyzed intermolecular formal [4 + 2] cycloaddition between 1a and benzaldehyde (Scheme 1)
To a stirred solution of 1a (77.4 mg, 0.398 mmol) and benzaldehyde (42.3 mg, 0.399 mmol) in dry dichloromethane (3 mL) was added at –45 °C boron trifluoride etherate (59 μL, 0.478 mmol), and the reaction mixture was stirred at –45 °C for 30 min and –20 °C for 3 h. The reaction was quenched by adding saturated aqueous ammonium chloride solution, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by preparative thin layer chromatography on silica gel (hexane / ethyl acetate = 5 : 1) to afford 2 (80.4 mg, 67%, cis / trans = 42 : 58) and 3 (13.5 mg, 13% yield).

(±)-(2R,6S)-3,3-Diallyl-6-ethoxy-2,3,5,6-tetrahydro-2-phenyl-4H-pyran-4-one (trans-2, the major isomer)

Colorless needles; mp 64.5-65.0 °C (EtOH-H2O); 1H NMR (500 MHz, CDCl3) δ 1.17 (t, J = 8.1 Hz, 3H), 1.77 (dd, J = 9.3, 15.4 Hz, 1H), 1.82 (dd, J = 7.1, 14.2 Hz, 1H), 2.54 (dd, J = 1.0, 15.1 Hz, 1H), 2.73 (dd, J = 7.6, 14.2 Hz, 1H), 2.76-2.80 (m, 1H), 2.84 (dd, J = 4.9, 15.1 Hz, 1H), 3.44 (qd, J = 7.1, 9.8 Hz, 1H), 3.64 (qd, J = 7.1, 10.0 Hz, 1H), 4.93-4.99 (m, 2H), 5.10-5.18 (m, 2H), 5.20 (s, 1H), 5.29-5.30 (m, 1H), 5.42-5.51 (m, 1H), 5.79-5.87 (m, 1H), 7.31-7.38 (m, 3H), 7.46-7.48 (m, 2H); 13C NMR (125 MHz, CDCl3) δ 14.9, 35.4, 37.2, 45.0, 56.8, 62.9, 73.5, 97.7, 118.0, 118.4, 127.8, 128.0, 128.1, 132.6, 135.1, 136.8, 207.0; IR (cm⁻¹, CHCl3) 2915, 1713, 1295, 1125, 1053, 1022, 994, 922; Anal. Calcd for C19H24O3: C, 75.97; H, 8.05. Found: C, 75.64; H, 8.17.
(±)-(2R,6R)-3,3-Diallyl-6-ethoxy-2,3,5,6-tetrahydro-2-phenyl-4H-pyran-4-one (cis-2, the minor isomer)

Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.24 (t, $J = 7.1$ Hz, 3H), 1.75-1.81 (m, 2H), 2.65-2.74 (m, 2H), 2.75-2.83 (m, 2H), 3.56 (qd, $J = 7.1$, 9.8 Hz, 1H), 3.98 (qd, $J = 7.1$, 9.8 Hz, 1H), 4.72 (s, 1H), 4.76 (dd, $J = 4.2$, 8.5 Hz, 1H), 4.94-5.00 (m, 2H), 5.12-5.18 (m, 2H), 5.41-5.49 (m, 1H), 5.71-5.79 (m, 1H), 7.31-7.38 (m, 3H), 7.47-7.49 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.1, 35.2, 36.9, 46.9, 56.7, 64.9, 77.3, 100.0, 118.5, 118.6, 127.8, 127.9, 128.0, 132.3, 134.9, 136.5, 207.5; IR (cm$^{-1}$, CHCl$_3$) 2982, 1711, 1638, 1377, 1354, 1123, 1048, 922; HRMS (EI+) m/z calcd for C$_{19}$H$_{24}$O$_3$: 300.17255, found 300.17305.

The stereochemistry was determined by NOE experiments.

3,3-Diallyl-2,3-dihydro-2-phenyl-4H-pyran-4-one (3)

Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.77 (dd, $J = 9.3$, 15.1 Hz, 1H), 1.93-1.98 (m, 1H), 2.51-2.56 (m, 1H), 2.84 (tdd, $J = 2.2$, 4.6, 15.1 Hz, 1H), 4.90-4.95 (m, 1H), 5.00-5.03 (m, 1H), 5.11-5.16 (m, 1H), 5.17-5.20 (m, 1H), 5.45 (s, 1H), 5.52 (d, $J = 5.9$ Hz, 1H), 5.55-5.64 (m, 1H), 5.70-5.78 (m, 1H), 7.38-7.40 (m, 3H), 7.42 (dd, $J = 0.5$, 5.9 Hz, 1H), 7.47-7.49 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 35.2, 35.5, 51.9, 86.2, 107.0, 118.6, 119.1, 128.1, 128.8, 132.5, 134.1, 134.8, 162.0, 195.2; IR (cm$^{-1}$, CHCl$_3$) 3013, 1669, 1605, 1406, 1254, 909; HRMS (EI+) m/z calcd for C$_{17}$H$_{18}$O$_2$: 254.13068, found 254.13048.
2.2 Ethylaluminum dichloride-catalyzed intramolecular formal [4 + 2] cycloaddition of 1a in the presence of benzaldehyde (Scheme 1)

To a stirred solution of 1a (101.5 mg, 0.522 mmol) and benzaldehyde (55.4 mg, 0.522 mmol) in dry dichloromethane (3 mL) was added at –45 °C a solution of ethylaluminum dichloride (1.04 M in hexane, 0.60 mL, 0.624 mmol), and the mixture was stirred at –45 °C for 15 min. The reaction was quenched by adding water, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (hexane / ether = 20 : 1 → 5 : 1 and benzene / ethyl acetate = 40 : 1) to afford 4a (66.7 mg, 66% yield, cis / trans = 79 : 21) and 2 (20.9 mg, 13% yield, cis / trans = 25 : 75) and 1a (7% recovery).

(±)-(1R,4S)-1-Allyl-4-ethoxybicyclo[4.1.0]heptan-2-one (cis-4a)

Colorless oil: ¹H NMR (500 MHz, CDCl₃) δ 1.07 (dd, J = 4.9, 8.5 Hz, 1H, H7exo × 1), 1.17 (t, J = 7.1 Hz, 3H, Me), 1.32 (dd, J = 5.1, 6.1 Hz, 1H, H7endo × 1), 1.43-1.48 (m, 1H, H6), 1.84 (ddd, J = 2.0, 7.8, 13.9 Hz, 1H, H5ax), 1.94 (dd, J = 6.6, 14.6 Hz, 1H, H1’), 2.31 (dd, J = 9.0, 14.6 Hz, 1H, H3ax), 2.33-2.39 (m, 1H, H5eq), 2.48 (ddd, J = 1.7, 4.4, 15.4 Hz, 1H, H3eq), 2.67 (dd, J = 6.8, 14.6 Hz, 1H, H1’), 3.46 (q, J = 7.1 Hz, 2H, OCH₂), 3.59-3.64 (m, 1H, H4), 4.96-5.01 (m, 2H, H3’), 5.72-5.80 (m, 1H, H2’); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 21.6, 22.8, 29.3, 33.7, 37.1, 43.4, 63.8, 75.4, 116.4, 135.3, 208.3; IR (cm⁻¹, CHCl₃) 3011, 1686, 1495, 1455, 1356, 1213, 1096, 1030; HRMS (El⁺) m/z calcd for C₁₂H₁₈O₂: 194.13068, found 194.13024.

The stereochemistry was determined by NOE experiments.
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(±)-(1R,4R)-1-Allyl-4-ethoxybicyclo[4.1.0]heptan-2-one (trans-4a)

Colorless oil: ¹H NMR (500 MHz, CDCl₃)  δ 1.00 (dd, J = 5.6, 8.5 Hz, 1H, H7exo), 1.04 (dd, J = 5.6, 6.1 Hz, 1H, H7endo), 1.16 (t, J = 7.1 Hz, 3H, Me), 1.53-1.58 (m, 1H, H6), 1.97 (dd, J = 6.6, 14.8 Hz, 1H, H1’), 1.98-2.04 (m, 1H, H5ax), 2.16 (ddd, J = 2.4, 4.2, 13.8 Hz, 1H, H5eq), 2.25 (ddd, J = 1.0, 7.8, 15.1 Hz, 1H, H3ax), 2.55 (dd, J = 4.2, 16.6 Hz, 1H, H3eq), 2.72 (dd, J = 6.7, 14.8 Hz, 1H, H1’), 3.42 (qd, J = 7.1, 9.0 Hz, 1H, CH₂ of Et), 3.49 (qd, J = 7.1, 9.0 Hz, 1H, CH₂ of Et), 3.67-3.71 (m, 1H, H4ax), 4.97-5.03 (m, 2H, H3’), 5.74-5.82 (m, 1H, H2’); ¹³C NMR (125 MHz, CDCl₃)  δ 15.4 (Me), 19.8 (C7), 22.0 (C6), 29.0 (C5), 33.0 (C1), 36.8 (C1’), 43.0 (C3), 63.4 (OCH₂), 73.2 (C4), 116.2 (C3’), 135.2 (C2’), 207.6 (C2); IR (cm⁻¹, CHCl₃) 3011, 2928, 1686, 1642, 1364; HRMS (EI+) m/z calcd for C₁₂H₁₈O₂: 194.13068, found 194.13075.

The stereochemistry was determined by NOE experiments.

2.3 A typical experimental procedure for EtAlCl₂-catalyzed intramolecular formal [4 + 2] cycloaddition of 2-alkenyl-3-ethoxycyclobutanones (Table 1, entry 1)
To a stirred solution of 1a (129.9 mg, 0.669 mmol) in dry dichloromethane (2 mL) was added a 1.04 M solution of EtAlCl\textsubscript{2} in hexane (0.77 mL, 0.801 mmol) at –45 °C, and the reaction mixture was stirred for 15 min at –45 °C. The reaction was quenched by adding water, and the mixture was 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 (hexane / ethyl acetate = 50 : 1 + 1% triethylamine) to afford 4a (119.1 mg, 92%) as a colorless oil. The ratio of cis-4a and trans-4a (cis / trans = 84 : 16) was determined by \textsuperscript{1}H NMR analysis of the obtained 4a. The cis-4a and trans-4a could be isolated by column chromatography on silica gel (hexane / ether). It should be noted that purification of the crude product by column chromatography on silica gel using an eluant without triethylamine caused the elimination of ethanol from 4a to give the corresponding enone.

\[\begin{align*} 
(\pm)-(1R,4S)-4\text{-Ethoxy-1-methylbicyclo[4.1.0]heptan-2-one (cis-4c)} \\
\text{Colorless oil: } \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) \delta 1.03 (dd, J = 4.6, 8.3 Hz, 1H, H7), 1.17 (t, J = 7.1 Hz, 3H, CH\textsubscript{2}CH\textsubscript{3}), 1.20 (s, 3H, Me), 1.33 (t, J = 5.1 Hz, 1H, H7), 1.40-1.45 (m, 1H, H6), 1.80 (ddd, J = 2.2, 8.1, 13.9 Hz, 1H, H5), 2.29 (dd, J = 9.3, 15.4 Hz, 1H, H3ax), 2.35-2.41 (m, 1H, H5), 2.51 (ddd, J = 1.7, 4.4, 15.1 Hz, 1H, H3eq), 3.46 (q, J = 7.1 Hz, 2H, OCH\textsubscript{2}), 3.59-3.65 (m, 1H, H4); 13C NMR (125 MHz, CDCl\textsubscript{3}) \delta 15.4, 19.3, 24.0, 24.8, 29.5, 29.9, 43.1, 63.8, 75.7, 209.5; IR (cm\textsuperscript{-1}, CHCl\textsubscript{3}) 2978, 1682, 1458, 1375, 1352, 1219, 1098, 909; HRMS (EI+) \textit{m/z} \text{calcd for C\textsubscript{10}H\textsubscript{16}O\textsubscript{2}: 168.11503, found 168.11520.} \\

The stereochemistry was determined by the similarity in \textsuperscript{1}H NMR spectra of cis-4a.

\[\begin{align*} 
(\pm)-(1R,4R)-4\text{-Ethoxy-1-methylbicyclo[4.1.0]heptan-2-one (trans-4c)} \\
\text{Colorless oil: } \text{\textsuperscript{1}H NMR (500 MHz, CDCl}_3) \delta 0.94 (dd, J = 5.1, 8.3 Hz, 1H, H7), 1.10 (t, J = 5.4 Hz, 1H, H7), 1.16 (t, J = 7.1 Hz, 3H, Me), 1.23 (s, 3H, Me), 1.51-1.55 (m, 1H, H6), 1.97-2.02 (m, 1H, H5), 2.15 (ddd, J = 2.4, 4.4, 13.7 Hz, 1H, H5), 2.26 (ddd, J = 1.0, 7.6, 16.8 Hz, 1H, H3), 2.55 (dd, J
= 4.2, 16.8 Hz, 1H, H3), 3.39-3.52 (m, 2H, OCH₂), 3.67-3.72 (m, 1H, H4); 13C NMR (125 MHz, CDCl₃) δ 15.5, 19.1, 21.4, 24.4, 29.1, 29.4, 42.6, 63.5, 73.4, 208.9; IR (cm⁻¹, CHCl₃) 2930, 1684, 1211, 1113; HRMS (EI+) m/z calcd for C₁₆H₂₀O₂: 244.1463, found 244.1464.

The stereochemistry was determined by the similarity in 1H NMR spectra of trans-4a.

(±)-(1R,4R)-1-Benzyl-4-ethoxybicyclo[4.1.0]heptan-2-one (cis-4d)

Colorless oil: 1H NMR (500 MHz, CDCl₃) δ 1.07 (dd, J = 4.9, 8.5 Hz, 1H, H7), 1.14 (t, J = 7.1 Hz, 3H, Me), 1.37 (dd, J = 5.1, 6.1 Hz, 1H, H7), 1.48-1.53 (m, 1H, H6), 1.86 (ddd, J = 2.0, 7.1, 14.2 Hz, 1H, H5eq), 2.27-2.32 (m, 1H, H5ax), 2.33 (dd, J = 8.3, 16.1 Hz, 1H, H3ax), 2.41 (ddd, J = 1.5, 4.4, 15.6 Hz, 1H, H3eq), 2.51 (d, J = 14.6 Hz, 1H, H1'), 3.41 (d, J = 14.6Hz, 1H, H1'), 3.42 (q, J = 7.1 Hz, 2H), 3.54-3.59 (m, 1H, H4), 7.14-7.26 (m, 5H, Ph); 13C NMR (125 MHz, CDCl₃) δ 15.4, 19.6, 22.0, 33.9, 37.8, 43.3, 63.4, 72.9, 126.0, 128.1, 129.1, 139.3, 207.6; IR (cm⁻¹, CHCl₃) 3011, 1686, 1356, 1096; HRMS (EI+) m/z calcd for C₁₆H₂₀O₂: 244.1463, found 244.1464.

The stereochemistry was determined by the similarity in 1H NMR spectra of cis-4a.

(±)-(1R,4S)-1-Benzyl-4-ethoxybicyclo[4.1.0]heptan-2-one (trans-4d)

Colorless oil: 1H NMR (500 MHz, CDCl₃) δ 0.99 (dd, J = 5.4, 8.5 Hz, 1H, H7), 1.07 (t, J = 5.7 Hz, 3H, Me), 1.11 (t, J = 7.1 Hz, 3H, Me), 1.57-1.61 (m, 1H), 1.98 (ddd, J = 5.6, 7.3, 13.7 Hz, 1H), 2.17 (ddd, J = 2.4, 4.2, 13.7 Hz, 1H), 2.21 (ddd, J = 0.7, 7.8, 16.8 Hz, 1H), 2.56 (d, J = 14.6 Hz, 1H, H1'), 2.58 (dd, J = 4.2, 16.8 Hz, 1H), 3.38 (qd, J = 7.1, 9.0 Hz, 1H, OCH₂), 3.44 (qd, J = 7.1, 9.0 Hz, 1H, OCH₂), 3.46 (d, J = 14.4 Hz, 1H, H1'), 3.64-3.69 (m, 1H, H4), 7.15-7.25 (m, 5H, Ph); 13C NMR (125 MHz, CDCl₃) δ 15.4, 19.6, 22.0, 28.8, 33.9, 37.8, 43.3, 63.4, 72.9, 126.0, 128.1, 129.3, 139.1, 207.6; IR (cm⁻¹, CHCl₃) 3011, 1686, 1455, 1364, 1107, 1088; HRMS (EI+) m/z calcd for C₁₆H₂₀O₂: 244.1463, found 244.1462.

The stereochemistry was determined by the similarity in 1H NMR spectra of trans-4a.
(±)-(1R,4R)-4-Ethoxy-1-isopropylbicyclo[4.1.0]heptan-2-one (cis-4e)

Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.85 (d, $J = 7.1$ Hz, 3H, H2'), 0.98 (d, $J = 6.8$ Hz, 3H, H2'), 1.08 (dd, $J = 5.1$, 8.8 Hz, 1H, H7), 1.15 (dd, $J = 5.1$, 6.1 Hz, 1H, H7), 1.16 (t, $J = 7.1$, 3H, CH$_2$CH$_3$), 1.33-1.38 (m, 1H), 1.81 (dd, $J = 2.2$, 8.1, 13.9 Hz, 1H), 1.85 (m, $J = 6.8$ Hz, 1H, H1'), 2.28 (ddd, $J = 0.5$, 9.0, 15.1 Hz, 1H), 2.31-2.37 (m, 1H), 2.44 (ddd, $J = 1.7$, 4.2, 15.1 Hz, 1H), 3.45 (qd, $J = 0.7$, 7.1 Hz, 2H, OCH$_2$CH$_3$), 3.55-3.60 (m, 1H, H4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.4, 18.0, 18.6, 20.1, 20.2, 29.2, 30.3, 37.9, 43.8, 63.3, 73.2, 208.3; IR (cm$^{-1}$, CHCl$_3$) 2979, 1686, 1456, 1383, 1109, 909; HRMS (EI+) m/z calcd for C$_{12}$H$_{20}$O$_2$: 196.14633, found 196.14647.

The stereochemistry was determined by the similarity in $^1$H NMR spectra of cis-4a.

(±)-(1R,4S)-4-Ethoxy-1-isopropylbicyclo[4.1.0]heptan-2-one (trans-4e)

Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.85 (d, $J = 7.1$ Hz, 3H, H2'), 0.89 (t, $J = 5.6$ Hz, 1H, H7), 1.00 (d, $J = 6.8$ Hz, 3H, H2'), 1.02 (dd, $J = 5.6$, 8.5 Hz, 1H, H2'), 1.15 (t, $J = 7.1$ Hz, 3H, OCH$_2$CH$_3$), 1.43-1.47 (m, 1H, H6), 1.92 (m, 1H, H1'), 1.97-2.02 (m, 1H, H5), 2.10-2.14 (m, 1H, H5), 2.21-2.27 (m, 1H, H3), 2.51 (dd, $J = 3.9$, 16.6 Hz, 1H, H3), 3.39-3.51 (m, 2H, OCH$_2$), 3.64-3.69 (m, 1H, H4); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.4, 18.0, 18.6, 20.1, 20.2, 29.2, 30.3, 37.9, 43.8, 63.3, 73.2, 208.3; IR (cm$^{-1}$, CHCl$_3$) 2979, 1686, 1456, 1383, 1109, 909; HRMS (EI+) m/z calcd for C$_{12}$H$_{20}$O$_2$: 196.14633, found 196.14601.

The stereochemistry was determined by the similarity in $^1$H NMR spectra of trans-4a.
1-Allyl-2-naphthol (7)\(^1\)

Colorless oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 3.82 (d, \(J = 5.6\) Hz, CH\(_2\)CH=), 5.05-5.11 (m, 3H, OH, =CH\(_2\)), 6.03-6.10 (m, 1H, CH\(_2\)CH=), 7.08 (d, \(J = 8.8\) Hz), 7.33 (t, \(J = 7.3\) Hz, 1H), 7.47 (t, \(J = 7.1\) Hz, 1H), 7.66 (d, \(J = 8.8\) Hz, 1H), 7.77 (d, \(J = 8.1\) Hz, 1H), 7.89 (d, \(J = 8.5\) Hz, 1H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 29.3, 116.0, 116.8, 117.9, 123.0, 123.2, 126.5, 128.3, 128.6, 129.4, 133.2, 135.7, 151.2; IR (cm\(^{-1}\), CHCl\(_3\)) 3588, 1620, 1516, 1260, 814.

(\(\pm\)-(1\(R\),4\(S\))-1-(3-Butenyl)-4-ethoxybicyclo[4.2.0]octan-2-one (9a)

Colorless oil: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.18 (t, \(J = 7.1\) Hz, 3H, Me), 1.67-1.73 (m, 2H, H5 and H1'), 1.77-1.87 (m, 3H, H7, H8, and H1''), 1.89-1.94 (m, 2H, H2'), 2.01-2.06 (m, 2H, H5 and H7), 2.32-2.37 (m, 1H, H8), 2.51 (ddd, \(J = 1.0, 6.8, 15.9\) Hz, 1H, H3), 2.51-2.55 (m, 1H, H6), 2.63 (ddd, \(J = 1.0, 4.4, 15.9\) Hz, 1H, H3), 3.47 (qd, \(J = 7.1, 9.0\) Hz, 1H, OCH\(_3\)), 3.51 (qd, \(J = 7.1, 9.0\) Hz, 1H, OCH\(_3\)), 3.84-3.88 (m, 1H, H4), 4.92-5.01 (m, 2H, H4') 5.71-5.79 (m, 1H, H3'); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 15.4 (Me), 23.4 (C7), 28.8 (C8), 29.0 (C2'), 32.6 (C5), 37.6 (C1'), 39.2 (C6), 45.0 (C3), 52.4 (C1), 63.6 (OCH\(_3\)), 75.8 (C4), 114.7 (C4'), 138.1 (C3'), 215.2 (C2); IR (cm\(^{-1}\), CHCl\(_3\)) 2930, 1701, 1642, 1451, 1354, 1210, 1084; HRMS (EI+) \(m/z\) calcld for C\(_{14}\)H\(_{22}\)O\(_2\): 222.16198, found 222.16149.

The stereochemistry was determined by NOE experiments.

(±)-(1R,4S)-4-Ethoxy-1-(4-pentenyl)bicyclo[4.3.0]nonan-2-one (9b)

Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.17 (t, $J = 7.1$ Hz, 3H, Me), 1.14-1.20 (m, 1H, H2'), 1.21-1.30 (m, 1H, H2'), 1.36 (ddd, $J = 5.4$, 8.8, 12.9 Hz, 1H, H9 x 1), 1.43-1.70 (m, 6H, H5 x 1, H1' x 2, H8 x 2, and H7 x 1), 1.82-1.90 (m, 1H, H7 x 1), 1.94-2.12 (m, 4H, H3' x 2, H5 x 1, and H6), 2.17 (ddd, $J = 9.3$, 10.2, 13.4 Hz, H9 x 1), 2.40 (dd, $J = 8.1$, 15.4 Hz, 1H, H3 x 1), 2.72 (ddd, $J = 1.7$, 5.1, 15.4 Hz, 1H, H3 x 1), 3.48 (qd, $J = 7.1$, 1.0 Hz, 2H, OCH$_2$), 3.68-3.74 (m, 1H, H4), 4.93-5.01 (m, 2H, H5' x 2), 5.72-5.80 (m, 1H, H4'); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.5 (Me), 22.1 (C8), 32.0 (C7), 33.6 (C5), 34.2 (C9), 34.2 (C6), 36.6 (C1'), 43.4 (C3'), 44.4 (C3), 59.1 (C1), 63.5 (OCH$_2$), 75.5 (C4), 114.7 (C5'), 138.5 (C4'), 213.4 (C2); IR (cm$^{-1}$, CHCl$_3$) 2939, 1698, 1640, 1458, 1375, 1356, 1235, 1102, 916; HRMS (EI+) m/z calcld for C$_{16}$H$_{26}$O$_2$: 250.19328, found 250.19373.

The stereochemistry was determined by NOE experiments.

(±)-(3R,4aR,9aR)-9a-Benzyl-3-ethoxy-3,4,4a,9,9a-hexahydro-1-(2H)-anthracenone (9d, the major isomer)

Colorless crystals: mp 125.5-126.0 °C (hexane-ether); $^1$H NMR (500 MHz, C$_6$D$_6$) $\delta$ 0.98 (t, $J = 7.1$ Hz, 3H, Me), 1.34 (ddd, $J = 2.7$, 12.5, 13.9 Hz, 1H, H4ax), 1.49-1.54 (m, 1H, H4eq), 2.09 (dd, $J = 2.7$, 17.6 Hz, 1H, H10), 2.31 (d, $J = 16.4$ Hz, 1H, H9), 2.32 (dd, $J = 15.8$, 4.2 Hz, 1H, H2), 2.45-2.50 (m, 1H, H4a), 2.54 (d, $J = 14.4$ Hz, 1H, Bn), 2.60 (dd, $J = 2.2$, 3.7, 15.9 Hz, 1H, H2), 2.81 (d, $J = 17.1$ Hz, 1H, H9), 2.89 (dd, $J = 6.3$, 17.6 Hz, H10ax), 3.00 (qd, $J = 6.8$, 8.8 Hz, 1H, OCH$_2$), 3.08 (qd,
$J = 7.1, 8.8 \text{ Hz, } 1H, \text{OCH}_2), 3.32-3.35 \text{ (m, } 1H, H3), 3.67 \text{ (d, } J = 14.4 \text{ Hz, } 1H, \text{Bn), 6.90-6.91 \text{ (m, } 1H), 6.95-6.97 \text{ (m, } 1H), 7.02-7.12 \text{ (m, } 5H), 7.20-7.21 \text{ (m, } 2H); ^{13}\text{C NMR (125 MHz, C}_6\text{D}_6) \delta 15.6 \text{ (Me), 30.2 (C4a), 31.4 (C10), 32.4 (C4), 34.7 (C9), 39.1 (Bn), 42.8 (C2), 52.7 (C9a), 63.0 (OCH}_2), 74.1 \text{ (C3), 126.3, 126.3, 126.4, 127.9, 128.1, 128.4, 129.6, 129.6, 130.8, 133.3 (C8a), 134.2 (C10a), 138.7(C2’), 210.9; IR (cm}^{-1}, \text{CHCl}_3) 3013, 1705, 1497, 1455, 1088, 702; \text{HRMS (EI+) m/z calcd for C}_{23}\text{H}_{26}\text{O}_2: 334.19328, \text{found 334.19268.} $

The stereochemistry was determined by X-ray crystallographic analysis.

CCDC 735720 contains the supplementary crystallographic data of this compound. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

$\text{C}_{23}\text{H}_{30}\text{O}_2, M = 334.46, \text{monoclinic, } a = 10.286(3), b = 16.713(4), c = 11.099(3) \text{ Å, } \beta = 112.789(2), U = 1759.0(7) \text{ Å}^3, T = 123 \text{ K, space group P121/a1 (no. 14), } Z = 4, 19979 \text{ reflections measured, 4596 unique (R}_{int} = 0.136), 2609 \text{ reflections (I > 3.0σ(I)) were used in all calculations. The final wR(F^2) was 0.0962 (I > 3.0σ(I)).}$

**Figure S1.** ORTEP figure of compound 9d. Thermal ellipsoids of non-H atoms are drawn at the
50% probability. H atoms are indicated by small circles.

(±)-(3R,4aS,9aS)-9a-Benzyl-3-ethoxy-3,4,4a,9,9a-hexahydro-1-(2H)-anthracenone (9d', the minor isomer)

Colorless crystals: mp 85.5-87.0 °C (EtOH); 1H NMR (500 MHz, C6D6) δ 0.98 (t, J = 7.1 Hz, 3H, Me), 1.46 (ddd, J = 9.5, 12.9, 13.2 Hz, 1H, H4ax), 1.52-1.56 (m, 1H, H4eq), 1.71-1.74 (m, 1H, H4a), 2.19 (d, J = 16.6 Hz, 1H, H10eq), 2.34 (d, J = 17.1 Hz, 1H, H9), 2.44 (d, J = 13.9 Hz, 1H, H1'), 2.48 (dd, J = 9.8, 15.4 Hz, 1H, H2ax), 2.63 (ddd, J = 1.7, 5.4, 15.4 Hz, 1H, H2eq), 2.90 (d, J = 17.1 Hz, 1H, H9), 3.01-3.10 (m, 3H, H3, H10ax, OCH2), 3.60 (d, J = 14.2 Hz, 1H, H1'), 6.85 (d, J = 7.3 Hz, 1H, arom), 7.00-7.21 (m, 8H, arom); 1H NMR (500 MHz, CDCl3) δ 1.12 (t, J = 7.1 Hz, 3H, Me), 1.62-1.70 (m, 1H, H4), 1.95-2.00 (m, 2H, H4 and H4a), 2.52-2.64 (m, 4H), 2.73 (ddd, J = 1.7, 5.6, 15.9 Hz, 1H, H2), 3.14 (d, J = 17.1 Hz, 1H, H1’ or H9), 3.21 (dd, J = 6.1, 17.3 Hz, 1H, H10), 3.43 (q, J = 7.1 Hz, 1H, OCH2), 3.43 (q, J = 7.1 Hz, 1H, OCH2), 3.47 (d, J = 14.4 Hz, 1H, H1’ or H9), 3.50-3.56 (m, 1H, H3), 7.07-7.25 (m, 9H, arom); 13C NMR (125 MHz, CDCl3) δ 15.5 (Me), 31.2 (C4a), 31.5 (C10), 34.4 (C4), 34.5 (C1’ or C9), 38.9 (C1’ or C9), 44.8 (C2), 52.1 (C9a), 63.5 (OCH2), 74.0 (C3), 126.1, 126.2, 126.3, 128.1, 129.2, 129.3, 130.4, 132.5, 133.5, 138.0, 212.6 (C1); 13C NMR (125 MHz, C6D6) δ 15.7 (Me), 31.2 (C4a), 31.7 (C10), 34.4 (C4), 34.7 (C9), 39.0 (C1’), 44.9 (C2), 52.2 (C9a), 63.3 (OCH2), 74.3 (C3), 126.3, 126.4, 126.5, 128.4, 129.5, 129.8, 131.0, 133.0 (C8a or C10a), 133.7 (C8a or C10a), 138.8, 211.0 (C1); IR (cm⁻¹, CHCl3) 3011, 1703, 1603, 1584, 1497, 1455, 1429, 1375, 1350, 1223, 1094, 740, 704; HRMS (EI+) m/z calcd for C23H26O2: 334.19328, found 334.19341.

The stereochemistry was determined by X ray crystallographic analysis.

CCDC 735721 contains the supplementary crystallographic data of this compound. This compound contains two enantiomers. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

C23H26O2, M = 334.46, orthorhombic, a = 7.3596(5), b = 19.161(1), c = 13.049(1) Å, U = 1840.1(2) Å³, T = 123 K, space group Pna21 (no. 33), Z = 4, 21633 reflections measured, 2648 unique (Rint = 0.017), 4049 reflections (unaveraged Friedel pairs, I > 3.0σ(I)) were used in all calculations. The final wR(F²) was 0.0443 (I > 3.0σ(I)).
Figure S2. ORTEP figure of compound 9d'. Thermal ellipsoids of non-H atoms are drawn at the 50% probability. H atoms are indicated by small circles.

The reaction of employing a mixture of four diastereomers of 8e (8ea : 8eb : 8ec : 8ed = 33 : 29 : 24 : 14) was performed at –45 °C for 25 min and 0 ºC for 5 min (Table 2, entry 5).

(±)-(1R,4S,4S,7S)-4-Ethoxytricyclo[5.4.0.01,6]undecan-2-one (cis-9e, the major diastereomer)
Colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.07-1.35 (m, 6H), 1.17 (t, $J = 7.1$ Hz, 3H, Me),
1.53-1.56 (m, 1H), 1.69 (ddd, J = 2.0, 8.8, 13.7 Hz, 1H, H5), 1.81-1.84 (m, 1H), 2.25 (dd, J = 10.5, 15.1 Hz, 1H, H3), 2.38-2.44 (m, 1H, H5), 2.52 (ddd, J = 2.0, 4.2, 14.9 Hz, 1H, H3), 2.69-2.74 (m, 1H), 3.43-3.49 (m, 2H), 3.53-3.59 (m, 1H, H4); 13C NMR (125 MHz, CDCl3) δ 15.4, 20.1, 21.0, 23.1, 23.2, 27.4, 30.0, 30.7, 33.8, 43.1, 63.7, 75.7, 208.9; IR (cm⁻¹, CHCl3) 2932, 1674, 1451, 1375, 1354, 1096, 669; HRMS (EI+) m/z calcd for C13H20O2: 208.14633, found 208.14599.

The stereochemistry was deduced by the similarity of 1H NMR spectra of cis-4a (chemical shifts and coupling patterns of H5).

(±)-(1R,4S,4R,7S)-4-Ethoxytricyclo[5.4.0.01,6]undecan-2-one (trans-9e, the minor diastereomer)

Colorless oil: 1H NMR (500 MHz, CDCl3) δ 0.83-0.90 (m, 1H), 1.16 (t, J = 7.1 Hz, 3H), 1.20-1.38 (m, 6H), 1.75-1.85 (m, 2H), 1.95-2.00 (m, 1H), 2.10-2.13 (m, 1H), 2.24-2.29 (m, 1H), 2.54 (dd, J = 4.2, 16.8 Hz, 1H), 2.67-2.73 (m, 1H), 3.38-3.52 (m, 2H), 3.68-3.72 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 15.5, 20.2, 20.9, 23.0, 23.1, 26.9, 27.7, 29.1, 30.3, 42.6, 63.4, 73.4, 208.4; IR (cm⁻¹, CHCl3) 2930, 1694, 1458, 1450, 1375, 1225, 1096; HRMS (EI+) m/z calcd for C13H20O2: 208.14633, found 208.14605.

The stereochemistry was deduced by the similarity of 1H NMR spectra of trans-4a.

(±)-(3R,4aS,6aR,10aS)-3-Ethoxy-dodecahydrobenzo[cd]inden-1-one (9f)

The reaction of employing a mixture of four diastereomers of 8f (33 : 23 : 23 : 21) was performed at −45 °C for 15 min and 0 °C for 15 min (Table 2, entry 6). Only one diastereomer was obtained. Colorless oil: 1H NMR (500 MHz, CDCl3) δ 1.17 (t, J = 7.1 Hz, 3H), 1.24-1.30 (m, 1H), 1.37-1.65 (m, 10H), 1.79-1.86 (m, 1H), 1.97-2.07 (m, 3H), 2.53 (dd, J = 9.3, 13.9 Hz, 1H, H2ax), 2.54-2.59 (m, 1H), 2.69 (ddd, J = 1.2, 4.6, 13.9 Hz, 1H, H2eq), 3.43-3.53 (m, 2H), 3.55-3.61 (m, 1H); 13C NMR (125 MHz, CDCl3) δ 15.5, 20.8, 22.5, 25.8, 26.5, 29.6, 30.0, 34.7, 40.0, 44.5, 44.7, 56.9, 63.6, 76.2, 214.3; IR (cm⁻¹, CHCl3) 2932, 1694, 1458, 1450, 1375, 1225, 1096; HRMS (EI+) m/z calcd for
C$_{15}$H$_{24}$O$_2$: 236.17763, found 236.17746.

The stereochemistry was determined by X-ray crystallography of a derivative of 9f which was prepared by reduction with sodium borohydride followed by the reaction with 3,5-dinitrobenzoyl chloride.

CCDC 735722 contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

C$_{22}$H$_{38}$N$_2$O$_7$, $M = 432.47$, triclinic, $a = 11.2136(2)$, $b = 11.4312(3)$, $c = 19.1419(7)$ Å, $\alpha = 85.877(4)$, $\beta = 75.202(4)$, $\gamma = 61.344(3)$, $U = 2078.0(1)$ Å$^3$, $T = 123$ K, space group P-1 (no. 2), $Z = 4$, 24749 reflections measured, 10170 unique ($R_{int} = 0.019$), 7267 reflections ($I > 3.0\sigma(I)$) were used in all calculations. The final $wR(F^2)$ was 0.054 ($I > 3.0\sigma(I)$).

**Figure S3.** ORTEP figure of a derivative of 9f. Thermal ellipsoids of non-H atoms are drawn at the 50% probability. H atoms are indicated by small circles.
2.4 Preparation of cyclobutanones

2.4.1 Preparation of 2,2-diallyl-3-ethoxycyclobutanone (1a)

2,2-Diallyl-3-ethoxycyclobutanone (1a)

To a stirred solution of 2-allylpent-4-enoyl chloride 16 (10.3 g, 64.9 mmol) in acetonitrile (100 mL) was added slowly a solution of ethyl vinyl ether (11.2 mL, 117 mmol) and triethylamine (11.0 mL, 78.9 mmol) in acetonitrile (30 mL) for 40 min. The resulting yellow suspension was stirred at 90 °C for 2 h. The cooled reaction mixture was then filtered through Celite and volatiles were evaporated. The crude product was purified by column chromatography on silica gel (hexane / ethyl acetate = 19 : 1 → 15 : 1 → 5 : 1) followed by distillation (80–84 °C / 2.5 mmHg) to afford 1a (6.11 g, 48%) as a colorless oil: 1H NMR (500 MHz, CDCl₃) δ 1.23 (t, J = 7.1 Hz, 3H), 2.29 (d, J = 7.3 Hz, 2H), 2.35 (dd, J = 8.1, 14.2 Hz, 1H), 2.53 (tdd, J = 1.2, 6.6, 14.4 Hz, 1H), 3.04 (dd, J = 5.9, 18.1 Hz, 1H), 3.13 (dd, J = 7.3, 18.1 Hz, 1H), 3.47-3.52 (m, 2H), 4.03 (dd, J = 5.6, 6.8 Hz, 1H), 5.06-5.14 (m, 4H), 5.68-5.77 (m, 1H), 5.82-5.90 (m, 1H); 13C NMR (125 MHz, CDCl₃) δ 15.2, 33.4, 36.8, 50.8, 65.6, 69.4, 71.0, 118.1, 118.8, 132.8, 133.9, 211.2; IR (cm⁻¹, CHCl₃) 2980, 1775, 1640, 1439, 1345, 1188, 1123, 999, 922; HRMS (El+) m/z calcd for C₁₂H₁₈O₂: 194.13068, found 194.13012.

2.4.2 Preparation of 2-allyl-3-ethoxycyclobutanone (1b)

2-Allyl-3-ethoxycyclobutanone (1b) was obtained in 10% yield from pent-4-enoyl chloride 17 by the procedure described in the preparation of 1a. The stereochemistry of 1b was determined by H3 chemical shifts according to Huisgen’s assignment.³ Compound 1b: 1H NMR (500 MHz, CDCl₃, a mixture of diastereomers, cis / trans = 30 : 70) δ 1.21 (t, J = 6.8 Hz, 0.9H, cis-Me), 1.24 (t, J = 7.1 Hz, 2.1H, trans-Me),

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2.27-2.33 (m, 0.7H), 2.39-2.50 (m, 1.4H), 2.92 (ddd, J = 1.7, 3.7, 17.6 Hz, 0.3H), 3.02 (ddd, J = 4.4, 5.6, 17.6 Hz, 0.7H), 3.13 (ddd, J = 2.0, 6.8, 17.5 Hz, 0.7H), 3.20 (ddd, J = 5.1, 6.3, 17.6 Hz, 0.3H), 3.30-3.39 (m, 1H), 3.45-3.56 (m, 2H, OCH₂), 3.96 (td, J = 5.1, 6.6 Hz, 0.7H, trans-H3), 4.30 (dt, J = 3.7, 6.6 Hz, 0.3H, cis-H3), 5.01-5.16 (m, 2H), 5.75-5.92 (m, 1H); ¹³C NMR (125 MHz, CDCl₃, a mixture of diastereomers, cis / trans = 30 : 70) δ 15.1 (cis), 15.2 (trans), 27.6 (cis), 31.7 (trans), 51.6 (trans), 52.3 (cis), 63.3 (cis), 65.2 (trans), 65.3 (cis), 65.9 (trans), 66.7 (cis), 69.1 (trans), 115.9 (cis), 117.1 (trans), 134.4 (trans), 135.9 (cis), 207.3 (trans), 209.0 (cis); IR (cm⁻¹, CHCl₃) 2980, 1781, 1642, 1341, 1123, 922; HRMS (EI⁺) m/z calcd for C₉H₁₄O₂: 154.09938, found 154.09967.

2.4.3 Preparation of 2-allyl-3-ethoxy-2-methylcyclobutanone (1c)

2-Methylpent-4-enoic acid (18)

2-Methylpent-4-enoic acid (18) was prepared by allylation of diethyl methylmalonate followed by hydrolysis and decarboxylation. ¹H NMR (500 MHz, CDCl₃) δ 1.19 (d, J = 7.1 Hz, 3H), 2.18-2.24 (m, 1H), 2.42-2.48 (m, 1H), 2.53-2.60 (m, 1H), 5.05-5.12 (m, 2H), 5.73-5.82 (m, 1H); ¹³C NMR (125 MHz, CDCl₃) δ 16.3, 37.5, 39.1, 117.2, 135.1, 182.3; IR (cm⁻¹, CHCl₃) 2980, 1709, 1649, 1496, 1244, 922; HRMS (EI⁺) m/z calcd for C₆H₁₀O₂: 114.06808, found 114.06836.

2-Allyl-3-ethoxy-2-methylcyclobutanone (1c)

Compound 1c was prepared from 2-methylpent-4-enoic acid (18) by formation of acid chloride with thionyl chloride, followed by [2 + 2] cycloaddition with ethyl vinyl ether using the method described in the preparation of 1a (51% yield for 2 steps). Compound 1c: ¹H NMR (500 MHz, CDCl₃, a mixture of diastereomers, cis / trans = 56 : 44) δ 1.16 (s, 1.68H, major Me), 1.18 (s, 1.32 H,
minor Me), 1.23 (t, J = 7.1 Hz, 1.32H, minor Me), 1.24 (t, J = 7.1 Hz, 1.68H, major Me), 2.25-2.30 (m, 0.88H, minor CH₂CH=CH₂), 2.34 (dd, J = 8.1, 14.2 Hz, 0.56H, major CH₂CH=CH₂), 2.48 (tdd, J = 1.2, 6.8, 14.2 Hz, 0.56H, major CH₂CH=CH₂), 3.03 (dd, J = 5.6, 17.8 Hz, 0.44H, minor H2), 3.07 (dd, J = 5.6, 17.3 Hz, 0.56H, major H2), 3.16 (dd, J = 7.1, 15.6 Hz, 0.56H, major H2), 3.20 (dd, J = 7.1, 15.1 Hz, 0.44H, minor H2), 3.46-3.57 (m, 2H, OCH₂), 3.88 (dd, J = 5.9, 6.8 Hz, 0.56H, major H3), 5.05-5.14 (m, 2H), 5.73-5.88 (m, 1H); ¹³C NMR (67.5 MHz, CDCl₃, a mixture of diastereomers, cis / trans = 56 : 44) δ 14.3, 15.1 (minor), 15.2 (major), 19.3, 35.4, 39.4, 50.2 (minor), 50.5 (major), 65.6 (minor), 65.6 (major), 65.9 (major), 66.3 (minor), 71.1, 73.9, 117.8 (major), 118.6 (minor), 133.0 (minor), 134.1 (major), 211.9 (major), 212.8 (minor); IR (cm⁻¹, CHCl₃) 1775, 1640, 1451, 1374, 1343, 1192, 1117, 922; HRMS (EI⁺) m/z calc. for C₁₀H₁₆O₂: 168.11503, found 168.11496.

The stereochemistry was determined by NOE.

2.4.4 Preparation of 2-allyl-2-benzyl-3-ethoxycyclobutanone (1d)

2-Benzylpent-4-enoic acid (19) was prepared by benzylation of diethyl allylmalonate, followed by hydrolysis and decarboxylation. ¹H NMR (500 MHz, CDCl₃) δ 2.27-2.32 (m, 1H), 2.36-2.42 (m, 1H), 2.75-2.81 (m, 2H), 2.96-3.01 (m, 1H), 5.06-5.11 (m, 2H), 5.74-5.82 (m, 1H), 7.17-7.22 (m, 3H), 7.26-7.30 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 35.6, 37.3, 46.9, 117.5, 126.5, 128.5, 128.9, 134.7, 138.8, 180.3; IR (cm⁻¹, CHCl₃) 3034, 1709, 1644, 1497, 1454, 922; HRMS (EI⁺) m/z calc. for C₁₂H₁₄O₂: 190.09938, found 190.09946.

2-Allyl-2-benzyl-3-ethoxycyclobutanone (1d)

Compound 1d was prepared as a colorless oil from 2-benzylpent-4-enoic acid (19) by formation of acid chloride with thionyl chloride, followed by [2 + 2] cycloaddition with ethyl vinyl ether using the method described in the preparation of 1a (35% yield for 2 steps): \(^1\)H NMR (500 MHz, CDCl\(_3\), a mixture of diastereomers, cis / trans = 34 : 66) \(\delta\) 1.16 (t, \(J = 7.1\) Hz, 1.0H, minor Me), 1.29 (t, \(J = 7.1\) Hz, 2.0H, major Me), 2.17 (dd, \(J = 7.6, 14.2\) Hz, 0.66H, major), 2.22 (dd, \(J = 7.1, 14.6\) Hz, 0.66H, major), 2.39 (dd, \(J = 8.1, 14.4\) Hz, 0.34H, minor), 2.57 (dd, \(J = 6.3, 14.4\) Hz, 0.34H, minor), 2.73 (d, \(J = 13.9\) Hz, 0.34H, minor), 2.84 (dd, \(J = 7.3, 18.1\) Hz, 0.34H, minor), 2.96-3.01 (m, 2H), 3.06-3.14 (m, 1.32H, major), 3.27 (qd, \(J = 7.1, 9.3\) Hz, 0.34H, minor O\(\text{CH}_2\)), 3.36 (qd, \(J = 7.1, 9.3\) Hz, 0.34H, minor O\(\text{CH}_2\)), 3.55 (q, \(J = 7.1\) Hz, 1.34H, major O\(\text{CH}_2\)), 4.02-4.07 (m, 1H, H3), 5.05-5.16 (m, 2H, =CH\(\text{H}_2\)), 5.68-5.76 (m, 0.67H, major CH=CH=CH=CH\(\text{H}_2\)), 7.14-7.30 (m, 5H); \(^13\)C NMR (125 MHz, CDCl\(_3\), a mixture of diastereomers, cis / trans = 34 : 66) \(\delta\) 15.1 (minor), 15.2 (major), 34.5 (minor), 34.6 (major), 36.9 (major), 38.5 (minor), 50.8 (minor), 50.9 (major), 65.4 (major), 65.4 (minor), 69.9, 70.5, 70.7 (minor), 70.7 (major), 118.3 (minor), 118.9 (major), 126.4 (major), 126.6 (minor), 128.0 (major), 128.4 (minor), 130.2 (minor), 130.4 (major), 133.1 (major), 134.1, 137.1, 210.8 (major), 211.5 (minor); IR (cm\(^{-1}\), CHCl\(_3\)) 2930, 1773, 1640, 1603, 1497, 1455, 1441, 1374, 1345, 1186, 1123, 1078, 924; HRMS (EI+) m/z calcd for C\(_{16}\)H\(_{20}\)O\(_2\): 244.14633, found 244.14674.

The stereochemistry of 1d was estimated by the fact that [2 + 2] cycloaddition between ketene and olefin gives cyclobutanones in which the bulkiest ketene and olefin substituents are in a 1,2-cis arrangement.\(^5\)

2.4.5 Preparation of 2-allyl-3-ethoxy-2-isopropylcyclobutanone (1e)

The stereochemistry of 1d was estimated by the fact that [2 + 2] cycloaddition between ketene and olefin gives cyclobutanones in which the bulkiest ketene and olefin substituents are in a 1,2-cis arrangement.\(^5\)

2-Isopropylpent-4-enoic acid (20)*

2-Isopropylpent-4-enoic acid (20) was prepared by isopropylation of diethyl allylmalonate, followed by hydrolysis and decarboxylation. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 0.98 (d, $J = 6.8$ Hz, 3H), 0.99 (d, $J = 6.8$ Hz, 3H), 1.89-1.96 (m, 1H), 2.23-2.38 (m, 3H), 5.01-5.04 (m, 1H), 5.07-5.11 (m,1H), 5.74-5.82 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 20.1, 20.2, 30.0, 33.6, 52.1, 116.7, 135.6, 180.6; IR (cm$^{-1}$, CHCl$_3$) 2967, 1705, 1644, 1441, 1231, 920; HRMS (EI+) $m/z$ calcd for C$_8$H$_{14}$O$_2$: 142.09938, found 142.09896.

2-Allyl-3-ethoxy-2-isopropylcyclobutanone (1e)

Compound 1e was prepared as a colorless oil from 2-isopropylpent-4-enoic acid (20) by chlorination of with thionyl chloride, followed by [2 + 2] cycloaddition with ethyl vinyl ether using the method described in the preparation of 1a (10% yield for 2 steps). Compound 1e: $^1$H NMR (500 MHz, CDCl$_3$, a mixture of diastereomers, cis / trans = 28 : 72) $\delta$ 0.89 (d, $J = 6.8$ Hz, 0.84H, cis-H2”), 0.93 (d, $J = 6.6$ Hz, 0.84H, cis-H2”), 1.02 (d, $J = 6.8$ Hz, 2.16H, trans-H2”), 1.05 (d, $J = 6.8$ Hz, 2.16H, trans-H2”), 1.22 (t, $J = 7.1$ Hz, 2.16H, trans-Me), 1.24 (t, $J = 7.1$ Hz, 0.84H, cis-Me), 1.94 (m, 0.28H, cis-H1”), 2.23-2.36 (m, 2.44H, trans-H1” + H1’ + trans-H1’), 2.52-2.56 (m, 0.28H, cis-H1”), 2.94 (dd, $J = 5.9$, 18.1 Hz, 0.72H, trans-H2), 2.96 (dd, $J = 5.9$, 18.3 Hz, 0.28H, cis-H2), 3.03 (dd, $J = 7.1$, 17.6 Hz, 0.72H, trans-H2), 3.05 (dd, $J = 7.3$, 18.1 Hz, 0.28H, cis-H2), 3.41-3.54 (m, 2H, OCH$_2$), 4.05 (dd, $J = 5.9$, 6.8 Hz, 0.72H, trans-H3), 4.09 (dd, $J = 5.9$, 7.3 Hz, 0.28H, cis-H3), 5.05-5.15 (m, 2H, H3’), 5.66-5.75 (m, 0.72H, trans-H2”), 5.86-5.94 (m, 0.28H, cis-H2’); $^{13}$C NMR (125 MHz, CDCl$_3$, a mixture of diastereomers, cis / trans = 28 : 72) $\delta$ 15.2 (cis + trans), 16.7 (cis), 18.2 (cis), 18.5 (trans), 18.9 (trans), 28.1 (trans), 28.8 (cis), 29.7 (trans), 30.3 (cis), 32.0 (cis), 34.4 (trans), 51.1 (cis), 51.3 (trans), 65.4 (trans), 68.7 (cis), 71.6 (trans), 73.2 (cis), 117.5 (cis), 118.5 (trans), 134.0 (trans), 134.6 (cis), 212.7 (cis), 212.8 (trans); IR (cm$^{-1}$, CHCl$_3$) 2990, 1769, 1640, 1387, 1190, 1119, 922; HRMS (EI+) $m/z$ calcd for C$_{12}$H$_{20}$O$_2$: 196.14633, found 196.14704.

For determination of the stereochemistry of 1e, see the determination of stereochemistry of 1d.

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2.4.6 Preparation of 2-allyl-3-ethoxy-2-phenylcyclobutanones (1f)

2-Phenylpent-4-enoic acid (21)\(^7\) was prepared by allylation of diethyl phenylmalonate followed by hydrolysis and decarboxylation.Compound 1f was synthesized from 2-phenylpent-4-enoic acid (21) by chlorination with thionyl chloride, followed by [2 + 2] cycloaddition with ethyl vinyl ether using the method of the synthesis of 1a (19% yield for 2 steps).

\[ \text{cis-1f} \]

\[ \text{trans-1f} \]

\((\pm)-(2R,3S)-2\text{-Allyl-3-ethoxy-2-phenylcyclobutanone (cis-1f):}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 1.31\) (t, \(J = 7.1 \text{ Hz}, 3\text{H})\), 2.66-2.70 (m, 1H), 2.78 (tdd, \(J = 1.2, 7.1, 14.4 \text{ Hz}, 1\text{H}\)), 3.15 (dd, \(J = 6.1, 17.8 \text{ Hz}, 1\text{H}\)), 3.22 (dd, \(J = 7.3, 18.0 \text{ Hz}, 1\text{H}\)), 3.63-3.69 (m, 2H), 4.43 (dd, \(J = 6.1, 7.3 \text{ Hz}, 1\text{H}\)), 4.86-4.91 (m, 1H), 4.94-4.96 (m, 1H), 5.68-5.76 (m, 1H), 7.21-7.25 (m, 1H), 7.31-7.38 (m, 4H); \(^1^3\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 15.3, 38.2, 50.7, 65.7, 73.6, 74.1, 118.0, 126.3, 126.8, 128.4, 133.5, 139.9, 208.5; IR (cm\(^{-1}\), CHCl\(_3\)) 2982, 1775, 1640, 1601, 1493, 1447, 1379, 1345, 1209, 1121, 1080, 1049, 922; HRMS (EI+) \(m/z\) calcd for C\(_{15}\)H\(_{18}\)O\(_2\): 230.13068, found 230.13072.

The stereochemistry was determined by NOE experiments.

\((\pm)-(2R,3R)-2\text{-Allyl-3-ethoxy-2-phenylcyclobutanone (trans-1f):}\) \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta \)

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1.07 (t, \(J = 7.1\) Hz, 3H), 2.62 (tdd, \(J = 1.2, 7.3, 14.2\) Hz, 1H), 2.69 (tdd, \(J = 1.2, 7.1, 14.2\) Hz, 1H), 3.01 (dd, \(J = 4.9, 18.1\) Hz, 1H), 3.31 (dd, \(J = 6.8, 18.1\) Hz, 1H), 3.36 (qd, \(J = 7.1, 9.3\) Hz, 1H, OCH\(\text{H}_2\)), 3.47 (qd, \(J = 7.1, 9.3\) Hz, 1H, OCH\(\text{H}_2\)), 4.23 (dd, \(J = 5.1, 6.8\) Hz, 1H, H3), 5.05-5.10 (m, 2H), 5.65-5.73 (m, 1H), 7.22-7.36 (m, 5H); \(^{13}\)C NMR (125 MHz, CDCl\(\text{3}\)) \(\delta\) 14.9, 41.9, 51.1, 65.4, 72.6, 74.2, 118.9, 126.9, 127.9, 128.0, 132.8, 136.0, 209.7; IR (cm\(^{-1}\), CHCl\(\text{3}\)) 2980, 1777, 1640, 1601, 1495, 1447, 1375, 1347, 1190, 1121, 1065, 924; HRMS (EI+) \(m/z\) calcd for C\(_{15}\)H\(_{18}\)O\(_2\): 230.13068, found 230.13021.

The stereochemistry was determined by NOE experiments. This assignment is consistent with Huisgen's assignment that the 3-H ring proton is more strongly deshielded by \textit{cis-vic-} than \textit{trans-vic-}alkyl group.

![Chemical structure](image)

2.4.7 Preparation of 2,2-di(but-3-enyl)-3-ethoxycyclobutanone (8a)

Diethyl dibut-3-enylmalonate (22)\(^8\)

To a stirred mixture of potassium hydroxide (9.81 g, 175 mmol) in DMSO (50 mL) was added at 0 °C trifluoromethanesulfonic acid (6.7 mL, 75.7 mmol),\(^9\) and the resulting mixture was stirred at room temperature for 15 min. 4-Bromo-1-butene (5.8 mL, 57.1 mmol) and diethyl malonate (4.0 g, 25.0 mmol) were added successively at room temperature, and the reaction mixture was stirred at 50 °C for 5.5 h. The reaction mixture was diluted with ether, and washed with 1 N hydrochloric acid, saturated aqueous sodium hydrogen carbonate, and water (four times). The organic layer was dried over anhydrous sodium sulfate and concentrated. The residue was purified by column

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chromatography on silica gel (hexane / ether = 10 : 1) to afford 22 (4.81 g, 17.9 mmol, 72% yield) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.25 (t, $J$ = 7.1 Hz, 6H), 1.93-2.02 (m, 8H), 4.19 (q, $J$ = 7.1 Hz, 4H), 4.95-4.98 (m, 2H), 5.01-5.06 (m, 2H), 5.75-5.83 (m, 2H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 14.1, 28.4, 31.6, 57.0, 61.1, 115.0, 137.6, 171.5; IR (cm$^{-1}$, CHCl$_3$) 2982, 1725, 1642, 1447, 1370, 1267, 1196, 1144, 1096, 1030, 918, 862; HRMS (EI+) $m/z$ calcd for C$_{15}$H$_{24}$O$_4$: 268.16746, found 268.16698.

2-(But-3-enyl)hex-5-enoic acid (23)

To a stirred solution of diethyl dibut-3-enylmalonate 22 (4.80 g, 17.9 mmol) in ethanol (30 mL) was added a solution of potassium hydroxide (3.01 g, 53.6 mmol) in H$_2$O (13 mL), and the mixture was refluxed for 12 h. After evaporation of the solvent, the residue was acidified to pH 2 with 1 N hydrochloric acid, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The obtained dibut-3-enylmalonic acid was heated at 155 °C for 4.5 h. The crude product was purified by column chromatography on silica gel (hexane / ether = 5 : 1) to afford 2-(but-3-enyl)hex-5-enoic acid 23 (2.82 g, 94% yield) as a colorless oil: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.55-1.62 (m, 2H), 1.73-1.81 (m, 2H), 2.04-2.17 (m, 4H), 2.41-2.47 (m, 1H), 4.97-5.00 (m, 2H), 5.02-5.06 (m, 2H), 5.75-5.83 (m, 1H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 31.1, 31.4, 44.0, 115.3, 137.6, 181.6; IR (cm$^{-1}$, CHCl$_3$) 2932, 1705, 1642, 1456, 1215, 995, 918; HRMS (EI+) $m/z$ calcd for C$_{10}$H$_{16}$O$_2$: 168.11503, found 168.11510.

2,2-Di(but-3-enyl)-3-ethoxycyclobutanone (8a)

To a stirred solution of 2-(but-3-enyl)hex-5-enoic acid 23 (1.01 g, 6.00 mmol) in dry dichloromethane (10 mL) was added at 0 °C thionyl chloride (1.3 mL, 17.8 mmol) and DMF (0.05 mL, 0.64 mmol), and the reaction mixture was stirred at room temperature for 1 h. After evaporation of the solvent, the obtained 2-(but-3-enyl)hex-5-enoic acid was used without purification.
To a stirred solution of thus-obtained 2-(but-3-enyl)hex-5-enoyl chloride in acetonitrile (5 mL) was slowly added at room temperature a solution of ethyl vinyl ether (1.0 mL) and triethylamine (0.99 mL) in acetonitrile (7 mL). The reaction mixture was heated at 90 °C for 2 h, and cooled reaction mixture was filtered through Celite pad. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane / ether = 35 : 1) to afford 1-(but-3-enyl)bicyclo[2.1.1]hexan-5-one (191.4 mg, 22%) and 8a (114.2 mg, 9%) as a colorless oil. 8a: 1H NMR (500 MHz, CDCl3) 1.23 (t, J = 7.1 Hz, 3H), 1.57-1.73 (m, 3H), 1.82 (dd, J = 4.9, 12.0, 14.1 Hz, 1H), 1.98-2.20 (m, 4H), 3.03 (dd, J = 5.6, 17.8 Hz, 1H), 3.16 (dd, J = 7.1, 17.8 Hz, 1H), 3.45-3.55 (m, 2H), 3.96 (dd, J = 5.6, 7.1 Hz, 1H), 4.93-4.99 (m, 2H), 5.01-5.06 (m, 2H), 5.76-5.85 (m, 1H); 13C NMR (125 MHz, CDCl3) 15.2, 27.4, 28.2, 28.7, 31.2, 50.8, 65.5, 69.8, 72.1, 114.6, 115.0, 137.8, 138.5, 212.2; IR (cm⁻¹, CHCl3) 2980, 1773, 1642, 1455, 1373, 1343, 1188, 1121, 995, 916; HRMS (EI⁺) m/z calcd for C14H22O2: 222.16198, found 222.16246.

2.4.8 Preparation of 3-ethoxy-2,2-di(pent-4-enyl)cyclobutanone (8b)

Diethyl 2,2-bis(5-phenylsulfanylpentyl)propanedioate (24)

Diethyl 2,2-bis(5-phenylsulfanylpentyl)propanedioate (24) was prepared from diethyl malonate and 5-bromo-1-phenylsulfanylpentane¹⁰ by using the method described in the preparation of diethyl dibut-3-enylmalonate 22 (61% yield). Compound 24: 1H NMR (500 MHz, CDCl3) 1.13-1.19 (m, 4H), 1.22 (t, J = 7.1 Hz, 6H), 1.39-1.45 (m, 4H), 1.60-1.67 (m, 4H), 1.82-1.86 (m, 4H), 2.89 (t, J =

7.3 Hz, 4H), 4.15 (q, J = 7.1 Hz, 4H), 7.13-7.17 (m, 2H), 7.25-7.32 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 14.1, 23.6, 28.8, 28.9, 32.1, 33.5, 57.4, 61.0, 125.7, 128.8, 128.9, 136.8, 171.7; IR (cm$^{-1}$, CHCl$_3$) 2934, 1723, 1586, 1482, 1439, 1228, 1157, 1094, 1026, 691; HRMS (EI+) m/z calcd for C$_{29}$H$_{40}$S$_2$O$_4$: 516.23681, found 516.23701.

7-Phenylsulfanyl-2-(5-phenylsulfanylpentyl)heptanoic acid (25)

To a solution of diethyl 2,2-bis(5-phenylsulfanylpentyl)propanedioate 24 (5.78 g, 11 mmol) in ethanol (70 mL) was added a solution of potassium hydroxide (3.76 g, 67 mmol) in water (30 mL), and the mixture was refluxed for 9 h. After evaporation of solvents, 1 N hydrochloric acid was added (pH 2), and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated. Thus-obtained 2,2-bis(5-phenylsulfanylpentyl)propanedioic acid was heated at 155 °C for 5 h. The crude product was purified by column chromatography on silica gel (hexane / ethyl acetate) to afford ethyl 7-phenylsulfanyl-2-(5-phenylsulfanylpentyl)heptanoate 26 (2.37 g, 48%) and 7-phenylsulfanyl-2-(5-phenylsulfanylpentyl)heptanoic acid 25 (2.24 g, 48%). Ethyl ester 26 was hydrolyzed to 25 by using potassium hydroxide in ethanol-water in 92% yield (total 92% yield).

7-Phenylsulfanyl-2-(5-phenylsulfanylpentyl)heptanoic acid (25): colorless crystals: mp 55.0-56.0 °C (hexane-ethyl acetate); $^1$H NMR (500 MHz, CDCl$_3$) δ 1.27-1.48 (m, 10H), 1.58-1.66 (m, 6H), 2.29-2.35 (m, 1H), 2.90 (t, J = 7.3 Hz, 4H), 7.14-7.17 (m, 2H), 7.25-7.32 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 26.8, 28.6, 28.9, 31.9, 33.5, 45.2, 125.7, 128.8, 128.9, 136.8, 182.3; IR (cm$^{-1}$, CHCl$_3$) 2936, 1705, 1586, 1482, 1439, 1292, 1157, 1094, 909, 691, 669; Anal. Calcd. For C$_{24}$H$_{32}$O$_2$S$_2$: C, 69.19; H, 7.74. Found: C, 68.93; H, 7.81.

3-Ethoxy-2,2-bis(5-phenylsulfanylpentyl)cyclobutanone (27)

3-Ethoxy-2,2-bis(5-phenylsulfanylpentyl)cyclobutanone (27) was prepared from 7-phenylsulfanyl-2-(5-phenylsulfanylpentyl)heptanoic acid (25) by chlorination with thionyl
chloride, followed by [2 + 2] cycloaddition with ethyl vinyl ether by the method described in the preparation of 1a (56% yield for 2 steps). Compound 27: 1H NMR (500 MHz, CDCl3) δ 1.21 (t, J = 7.1 Hz, 3H), 1.24-1.70 (m, 16H), 2.90 (t, J = 6.8 Hz, 4H), 2.98 (dd, J = 5.6, 18.1 Hz, 1H), 3.11 (dd, J = 7.1, 17.8 Hz, 1H), 3.41-3.52 (m, 2H), 3.89 (dd, J = 5.9, 6.8 Hz, 1H), 7.14-7.18 (m, 2H), 7.25-7.32 (m, 8H); 13C NMR (125 MHz, CDCl3) δ 15.2, 23.6, 24.0, 28.0, 28.9, 29.0, 29.2, 29.4, 32.0, 33.5, 50.7, 65.4, 70.2, 72.1, 125.7, 125.8, 128.8, 128.9, 129.0, 136.8, 136.9, 212.8; IR (cm⁻¹, CHCl3) 2936, 1771, 1586, 1482, 1439, 1120, 691; HRMS (EI+) m/z calcd for C28H38S2O2: 470.23133, found 470.23090.

3-Ethoxy-2,2-di(pent-4-enyl)cyclobutanone (8b)

To a stirred solution of 3-ethoxy-2,2-bis(5-phenylsulfanylpentyl)cyclobutanone 27 (501 mg, 1.07 mmol) in dichloromethane (6 mL) was added at 0 °C a solution of mCPBA (65%, 563 mg, 2.12 mmol) in dichloromethane (4 mL), and the mixture was stirred at 0 °C for 15 min. The reaction was quenched with 10% aqueous Na2S2O3 solution, and the mixture was extracted with dichloromethane. The combined organic extracts were washed with saturated aqueous sodium hydrogencarbonate solution, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 1 : 3 → ethyl acetate only) to afford 3-ethoxy-2,2-bis(5-phenylsulfinylpentyl)cyclobutanone 28 (430.5 mg, 80%).

A mixture of 28 (430.5 mg, 0.856 mmol) and sodium hydrogencarbonate (360 mg, 4.28 mmol) in xylene (7 mL) was refluxed for 14 h. Water was added to the cooled reaction mixture, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate = 30 / 1 → 15 / 1) to afford 8b (191.3 mg, 89%) as a pale yellow oil: 1H NMR (500 MHz, CDCl3) δ 1.22 (t, J = 7.1 Hz, 3H, Me), 1.30-1.74 (m, 8H), 2.02-2.07 (m, 4H), 3.00 (dd, J = 5.6, 17.8 Hz, 1H, H2), 3.13 (dd, J = 7.1, 18.1 Hz, 1H, H2), 3.44-3.54 (m, 2H, OCH2), 3.91 (dd, J = 5.6, 7.1 Hz, 1H, H3), 4.93-5.03 (m, 4H, CH=CH2), 5.74-5.83 (m, 2H, CH=CH2); 13C NMR (125 MHz, CDCl3) δ 15.2, 23.3, 23.7, 27.6, 31.6, 34.0, 34.2, 50.7, 65.4, 70.3, 72.2, 114.6, 115.0, 138.2, 138.5, 212.7; IR (cm⁻¹, CHCl3) 2940, 1771, 1640, 1458, 1373, 1343, 1215, 1186, 1121, 916; HRMS (EI+) m/z calcd for C18H38O2: 250.19328, found 250.19399.
2.4.9 Preparation of 3-ethoxy-2,2-di(hex-5-enyl)cyclobutanone (8c)

Compound 8c was prepared by the method described in the synthesis of 8b.

Diethyl 2,2-bis(6-phenylsulfanylhexyl)propanedioate (29)

\(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.10-1.17 (m, 4H), 1.23 (t, \(J = 7.1\) Hz, 6H), 1.27-1.33 (m, 4H), 1.39-1.45 (m, 4H), 1.60-1.66 (m, 4H), 1.82-1.85 (m, 4H), 2.90 (t, \(J = 7.3\) Hz, 4H), 4.16 (q, \(J = 7.1\) Hz, 4H), 7.14-7.17 (m, 2H), 7.25-7.32 (m, 8H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 14.1, 23.8, 28.5, 29.1, 29.4, 32.1, 33.5, 57.4, 61.0, 125.7, 128.8, 128.8, 136.9, 171.9; IR (cm\(^{-1}\), CHCl\(_3\)) 2932, 1723, 1586, 1482, 1439, 1257, 1209, 1156, 1094, 1026, 691; HRMS (EI+) \(m/z\) calcd for C\(_{31}\)H\(_{44}\)S\(_2\)O\(_4\): 544.26811, found 544.26786.

8-Phenylsulfanyl-2-(phenylsulfanylhexyl)octanoic acid (30)

Colorless needles: mp 102.5-103.0 °C (hexane-ethyl acetate); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 1.25-1.35 (m, 8H), 1.38-1.48 (m, 6H), 1.60-1.66 (m, 6H), 2.29-2.35 (m, 1H), 2.90 (t, \(J = 7.3\) Hz, 4H), 7.13-7.17 (m, 2H), 7.25-7.32 (m, 8H); \(^13\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 27.2, 28.6, 29.0, 29.0, 32.0, 33.5, 45.4, 125.6, 128.8, 128.9, 136.9, 182.5; IR (cm\(^{-1}\), CHCl\(_3\)) 2934, 1705, 1586, 1482, 1439, 691; Anal. Calcd. For C\(_{26}\)H\(_{36}\)O\(_2\)S\(_2\): C, 70.22; H, 8.16. Found: C, 69.98; H, 8.29.
3-Ethoxy-2,2-bis(6-phenylsulfanylhexyl)cyclobutanone (31)

Colorless oil; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.22 (t, $J$ = 7.1 Hz, 3H, Me), 1.26-1.70 (m, 20H), 2.90 (t, $J$ = 7.3 Hz, 2H, SCH$_2$), 2.91 (t, $J$ = 7.6 Hz, 2H, SCH$_2$), 2.99 (dd, $J$ = 5.9, 17.8 Hz, 1H, H2), 3.12 (dd, $J$ = 6.8, 17.8 Hz, 1H, H2), 3.42-3.52 (m, 2H, OCH$_2$), 3.89 (dd, $J$ = 5.9, 6.8 Hz, 1H, H3), 7.14-7.18 (m, 2H), 7.26-7.32 (m, 8H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.2, 23.8, 24.2, 28.0, 28.6, 28.6, 29.0, 29.1, 29.5, 29.7, 32.0, 33.5, 50.6, 65.4, 70.3, 72.2, 77.2, 125.6, 125.7, 128.8, 128.8, 128.8, 128.9, 136.9, 137.0, 212.8; IR (cm$^{-1}$, CHCl$_3$) 2934, 1771, 1586, 1482, 1439, 1186, 1119, 752, 691, 669; HRMS (EI+) m/z calcd for C$_{30}$H$_{42}$S$_2$O$_2$: 498.26263, found 498.26196.

3-Ethoxy-2,2-di(hex-5-enyl)cyclobutanone (8c)

$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.23 (t, $J$ = 6.8 Hz, 3H), 1.22-1.73 (m, 12H), 2.03-2.08 (m, 2H, CH$_2$CH=CH$_2$), 3.00 (dd, $J$ = 5.6, 17.8 Hz, 1H, H2), 3.13 (dd, $J$ = 7.1, 17.8 Hz, 1H, H2), 3.44-3.54 (m, 2H, OCH$_2$), 3.91 (dd, $J$ = 5.6, 6.8 Hz, 1H, H3), 4.92-5.02 (m, 4H, CH=CH$_2$), 5.75-5.84 (m, 2H, CH=CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.2, 23.4, 23.9, 27.9, 29.2, 29.5, 31.9, 33.5, 33.5, 50.7, 65.4, 70.4, 72.2, 114.3, 114.5, 138.6, 138.9, 212.9; IR (cm$^{-1}$, CHCl$_3$) 2936, 1771, 1640, 1462, 1372, 1343, 1186, 1121, 995, 914; HRMS (EI+) m/z calcd for C$_{18}$H$_{30}$O$_2$: 278.22458, found 278.22421.
2.4.10 Preparation of 2-(o-allylbenzyl)-2-benzyl-3-ethoxycyclobutanone (8d)

To a stirred solution of sodium ethoxide in ethanol which was prepared by using sodium (424 mg) and absolute ethanol (50 mL) was added at 70 °C diethyl benzylmalonate (3.33 mL, 14.2 mmol). 2-Iodobenzyl bromide (5.70 g, 19.2 mmol) in absolute ethanol (35 mL) was then added, and the mixture was stirred at 70 °C for 40 min. After evaporation of the solvent, water was added, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated. To a stirred solution of thus-obtained product in ethanol (40 mL) was added a solution of potassium hydroxide (4.77 g, 85.0 mmol) in water (30 mL), and the mixture was refluxed for 9 h. After evaporation of the solvent, the residue was washed with ether. The aqueous phase was acidified with 1 N hydrochloric acid, and the mixture was extracted with ether. The concentrated product was purified by column chromatography on silica gel (hexane / ethyl acetate = 2 : 1) to afford 2-benzyl-3-(o-iodophenyl)propanoic acid (8d) (3.70 g, 71% for 3 steps) as colorless crystals: mp 108.0-108.5 °C (hexane-ethyl acetate); 1H NMR (500 MHz, CDCl 3 ) δ 2.86 (dd, J = 5.9, 13.7 Hz, 1H), 2.93 (dd, J = 4.6, 13.2 Hz, 1H), 3.02-3.14 (m, 3H), 6.88-6.91 (m, 1H), 7.19-7.29 (m, 7H), 7.81 (d, J = 7.8 Hz, 1H); 13C NMR (125 MHz, CDCl 3 ) δ 38.2, 42.4, 47.5, 100.6, 126.6, 128.3,
128.4, 128.9, 130.3, 138.3, 139.7, 141.4, 179.7; IR (cm⁻¹, CHCl₃) 3021, 1709, 1223, 1210, 1013, 700, 699; Anal. Calcd. For C₁₆H₁₅IO₂: C, 52.48; H, 4.13. Found: C, 52.42; H, 4.09.

**2-Benzyl-3-ethoxy-2-(o-iodobenzyl)cyclobutanone (33)**

To a stirred solution of 2-benzyl-3-(o-iodophenyl)propanoic acid 32 (3.70 g, 10.1 mmol) in dichloromethane (40 mL) was added at 0 °C thionyl chloride (2.2 mL, 30.2 mmol) and DMF (0.08 mL, 1.03 mmol), and the mixture was stirred at room temperature for 2 h. After evaporation of volatiles, dry acetonitrile (30 mL) was added. To this solution was added a mixture of ethyl vinyl ether (3.5 mL, 36.5 mmol) and triethylamine (3.4 mL, 24.4 mmol) in acetonitrile (20 mL), and the reaction mixture was stirred at 90 °C for 3 h. Water was added, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (hexane / ethyl acetate) to afford 33 (3.61 g, 85% for 2 steps). ^1H NMR (500 MHz, CDCl₃, a mixture of diastereomers, 50 : 50) δ 1.27 (t, J = 7.1 Hz, 1.5H, Me), 1.27 (t, J = 7.1 Hz, 1.5H, Me), 2.70 (dd, J = 7.1, 18.1 Hz, 0.5H, H₂), 2.73 (dd, J = 7.1, 18.1 Hz, 0.5H, H₂), 2.79 (d, J = 13.9 Hz, 0.5H), 2.89 (dd, J = 5.9, 17.8 Hz, 0.5H, H₂), 2.93-2.99 (m, 1.5H), 3.06 (dd, J = 5.6, 17.8 Hz, 0.5H, H₂), 3.14 (d, J = 14.4 Hz, 0.5H), 3.20 (d, J = 14.2 Hz, 0.5H), 3.30 (d, J = 15.1 Hz, 0.5H), 3.37 (d, J = 14.9 Hz, 0.5H), 3.49-3.56 (m, 2H, OCH₂), 3.98 (t, J = 6.3 Hz, 0.5H, H), 4.04 (dd, J = 5.9, 6.8 Hz, 0.5H, H), 6.87 (dd, J = 1.5, 7.8 Hz, 0.5H), 6.91 (dd, J = 1.5, 7.8 Hz, 0.5H), 7.04-7.06 (m, 1H), 7.12 (dd, J = 1.2, 7.8 Hz, 0.5H), 7.17-7.33 (m, 5H), 7.49 (dd, J = 1.2, 7.8 Hz, 0.5H), 7.82 (d, J = 8.1 Hz, 0.5H), 7.84 (d, J = 8.1 Hz, 0.5H); ^13C NMR (125 MHz, CDCl₃, a mixture of diastereomers, 50 : 50) δ 15.2, 15.3, 36.5, 38.4, 39.6, 42.8, 51.2, 51.8, 65.6, 69.3, 69.5, 71.5, 71.5, 103.1, 103.2, 126.5, 126.6, 128.0, 128.2, 128.2, 128.3, 128.4, 130.2, 130.6, 130.8, 131.0, 137.0, 137.1, 139.6, 139.7, 140.5, 140.6, 210.5, 211.1; IR (cm⁻¹, CHCl₃) 3011, 1773, 1437, 1345, 1184, 1121, 1013, 702; HRMS (EI⁺) m/z calcd for C₂₀H₂₁O₂I: 420.05866, found 420.05848.
2-(α-Allylbenzyl)-2-benzyl-3-ethoxycyclobutanone (8d)

To the mixture of LiCl (60.5 mg, 1.43 mmol), Pd(PPh₃)₄ (29 mg, 25 μmol), and CuCl (124 mg, 1.25 mmol) was added a solution of 33 (98.7 mg, 0.235 mmol) in DMSO (4 mL). Allyltributylstannane (0.09 mL, 0.29 mmol) was then added, and the reaction mixture was stirred at room temperature for 1 h and at 60 °C for 10 h. The reaction mixture was cooled, and 5% aqueous NH₄OH and brine were added. The resulting mixture was extracted with ether, and the combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on 10% w/w KF and silica gel (hexane / ethyl acetate = 25 : 1) to afford 8d (55.3 mg, 70%) as a mixture of two diastereomers (53 : 47): 1H NMR (500 MHz, CDCl₃, a mixture of diastereomers, 53 : 47) δ 1.26 (t, J = 6.8 Hz, 1.4H, minor Me), 1.28 (t, J = 7.1 Hz, 1.6H, major Me), 2.67-3.53 (m, 11H), 3.92 (t, J = 6.1 Hz, 0.53H, major H3), 4.05 (t, J = 6.1 Hz, 0.47H, minor H3), 4.80-5.05 (m, 2H), 5.77-5.94 (m, 1H), 7.05-7.44 (m, 9H); 13C NMR (125 MHz, CDCl₃, a mixture of diastereomers, 53 : 47) δ 15.2, 15.2, 31.1, 34.7, 36.5, 37.3, 37.6, 39.3, 51.2, 51.3, 65.1, 65.3, 69.6, 70.1, 71.4, 71.8, 115.7, 115.8, 126.1, 126.4, 126.5, 126.6, 126.8, 128.0, 128.4, 129.7, 129.7, 130.2, 130.6, 130.6, 131.1, 135.7, 135.8, 136.7, 137.1, 137.3, 138.8, 138.9, 211.0, 211.2; IR (cm⁻¹, CHCl₃) 2980, 1773, 1219, 669; HRMS (EI⁺) m/z calcd for C₂₃H₂₆O₂: 334.19328, found 334.19294.

2.4.11 Preparation of 3-ethoxy-5-vinylspiro[3.5]nonan-1-one (8e)

![Chemical structure](image)

3-Ethoxy-5-vinylspiro[3.5]nonan-1-one (8e)

To a stirred solution of (±)-(1R,2R)-2-vinylcyclohexanecarboxylic acid¹² 34 (1.33 g, 8.60 mmol) in dry dichloromethane (15 mL) was added at 0 °C oxalyl chloride (1.1 mL, 13.0 mmol), and the mixture was stirred at room temperature for 1 h. After evaporation of volatiles, dry acetonitrile (13 mL) was added. To this solution was added a solution of ethyl vinyl ether (3.0 mL, 31.3 mmol) and triethylamine (2.9 mL, 20.8 mmol) in acetonitrile (7 mL) for 30 min. The resulting reaction mixture was stirred at 90 °C for 3 h. Water was added to the cooled reaction mixture, and the mixture was extracted with ether. The combined organic extracts were washed with brine, dried, and concentrated. The residue was purified by column chromatography on silica gel (hexane /

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¹¹ Han, X.; Stoltz, B. M.; Corey, E. J. J. Am. Chem. Soc. 1999, 121, 7600.
ether and hexane / dichloromethane) to afford 8e (772 mg, 3.71 mmol, 43% combined yield for 2 steps) as a mixture of four diastereomers (8ea : 8eb : 8ec : 8ed = 33 : 29 : 24 : 14). The ratio of diastereomer (8ea-d) was determined by $^1$H NMR spectra.

The major isomer 8ea: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 1.24 (t, $J = 7.1$ Hz, 3H, Me), 1.27-1.34 (m, 1H), 1.43-1.75 (m, 6H), 1.81-1.86 (m, 1H), 2.58-2.62 (m, 1H), 2.92 (dd, $J = 6.1$, 17.6 Hz, 1H, H2), 3.12 (dd, $J = 7.1$, 17.8 Hz, 1H, H2), 3.54 (q, $J = 7.1$ Hz, 1H, OCH$_3$), 3.54 (q, $J = 7.1$ Hz, 1H, OCH$_3$), 3.83 (dd, $J = 6.3$, 7.1 Hz, 1H, H3), 5.03-5.07 (m, 2H, CH=CH$_2$), 6.14-6.21 (m, 1H, CH=CH$_2$); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 15.3, 22.3, 23.4, 28.7, 31.5, 40.3, 50.9, 65.4, 70.7, 74.8, 114.9, 139.9, 212.0; IR (cm$^{-1}$, CHCl$_3$) 2936, 1767, 1636, 1449, 1192, 1123, 912; HRMS (EI+) m/z calcd for C$_{13}$H$_{20}$O$_2$: 208.14633, found 208.14695.

The relative stereochemistry of 8ea was not determined.

2.4.12 Preparation of 5-(but-3-enyl)-3-ethoxyspiro[3.5]nonan-1-one (8f)
2-[(p-methoxybenzyl)methyl]cyclohexanecarboxaldehyde (37)

To a stirred suspension of NaH (1.51 g, 60%, 37.8 mmol, washed with hexane) in dry DMF (20 mL) was added a solution of cis-1,2-cyclohexanediol 35 (5.43 g, 37.7 mmol) in dry DMF (15 mL) at room temperature, and the mixture was stirred at room temperature for 40 min. PMBCl (5.11 mL, 37.7 mmol) was added to the reaction mixture at 0 °C, and the mixture was stirred at room temperature for 1 h. Water was added to the reaction mixture, and the mixture was extracted with ethyl acetate. The combined organic extracts were washed with water, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 10 : 1 → 4 : 1 → 1 : 1) to afford 2-[(p-methoxybenzyloxy)methyl]cyclohexyl]methanol 36 (6.09 g, 61%) as a colorless oil.

To a stirred solution of oxalyl chloride (3.87 mL, 45.7 mmol) in dichloromethane (160 mL) was added a solution of DMSO (6.51 mL, 91.7 mmol) in dichloromethane (10 mL) at –78 °C. A solution of 36 (6.06 g, 22.9 mmol) in dichloromethane (10 mL) was then added to the mixture at –78 °C, and the reaction mixture was stirred at –78 °C for 15 min. Triethylamine (32 mL, 230 mmol) was added to the mixture, and the resulting mixture was stirred for at room temperature for 30 min. After addition of water, the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 6 : 1) to afford 37 (5.70 g, 95%) as a pale yellow oil: 

\[ \text{1H NMR} (500 \text{ MHz, CDCl}_3) \delta 1.37-1.81 \text{ (m, 8H), 2.29-2.35 \text{ (m, 1H), } 2.51-2.54 \text{ (m, 1H), } 3.44 \text{ (dd, } J = 5.9, 9.3 \text{ Hz, 1H), } 3.54 \text{ (dd, } J = 8.7, 9.0 \text{ Hz, 1H), } 3.80 \text{ (s, 3H), } 4.38 \text{ (s, 2H), } 6.85-6.88 \text{ (m, 2H), } 7.20-7.23 \text{ (m, 2H), } 9.75 \text{ (s, 1H); } \text{13C NMR} (125 \text{ MHz, } \text{CDCl}_3) \delta 23.3, 23.5, 24.0, 27.3, 37.5, 50.3, 55.2, 70.7, 72.8, 113.7, 129.2, 130.3, 159.1, 204.5; \text{IR (cm}^{-1}, \text{CHCl}_3) 3019, 1717, 1613, 1514, 1248, 1084, 1036; \text{HRMS (El+) m/z} \text{ calcld for } C_{16}H_{22}O_3: 262.15690, \text{ found } 262.15604. \]

1-[4-(benzyloxy)butyl]-2-[(p-methoxybenzyloxy)methyl]cyclohexane (39)

To a stirred suspension of [3-(benzyloxy)propyl]triphenylphosphonium bromide\(^\text{13}\) (10.8 g, 22.0 mmol) in dry THF (230 mL) was added a solution of sodium hexamethyldisilazide (1.90 N in THF, 10.5 mL, 20.0 mmol) at 0 °C, and the resulting mixture was stirred at room temperature for 15 min. A solution of 37 (5.23 g, 19.9 mmol) in THF (8 mL) was added at 0 °C, and the mixture was stirred

at 0 °C for 30 min. After evaporation of the solvent, the residue was filtered through Celite pad and the solid was washed with ether. The filtrate was concentrated, and the residue was purified by column chromatography on silica gel (hexane only → hexane / ethyl acetate = 20 : 1 → 5 : 1) to afford 1-[4-(benzyl oxy)but-1-enyl]-2-[(p-methoxybenzyl oxy)methyl]cyclohexane 38 (7.26 g, 92%) as a pale yellow oil.

To the solution of 38 (7.26 g, 18.4 mmol) in EtOH (150 mL) was added Pd/C-ethylelediamine complex14 (730.4 mg). Under H2 atmosphere (1 atm, balloon), the suspension was stirred at room temperature for 24 h. The reaction mixture was filtered through Celite pad, and the filtrate was concentrated to give 39 (7.10 g, 97%) as a pale yellow oil: 1H NMR (500 MHz, CDCl3, two conformers) δ 1.01-1.86 (m, 16H), 3.20-3.40 (m, 4H), 3.72 (s, 3H), 4.28-4.38 (m, 2H), 4.42 (s, 2H), 6.78-6.81 (m, 2H), 7.16-7.27 (m, 7H); 13C NMR (125 MHz, CDCl3, two conformers) δ 22.9, 24.2, 26.4, 28.7, 30.0, 33.3, 39.3, 42.2, 55.3, 70.5, 72.6, 72.7, 72.9, 113.7, 113.7, 127.4, 127.6, 128.3, 129.1, 129.1, 131.0, 138.7, 159.1; IR (cm⁻¹, CHCl3) 2932, 1613, 1514, 1455, 1364, 1302, 1248, 1094, 1036; HRMS (EI+) m/z calcd for C26H36O3: 396.26645, found 396.26611.

2-[4-(benzyl oxy)butyl]cyclohexanecarboxylic acid (41)

To a stirred mixture of 39 (6.84 g, 17.2 mmol) in dichloromethane (150 mL) and water (70 mL) was added DDQ (4.8 g, 21.1 mmol) at room temperature, and the mixture was stirred at room temperature for 1 h. After addition of 10% aqueous Na2S2O3 solution, the mixture was extracted with dichloromethane. The combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel to afford 2-[4-(benzyl oxy)butyl]cyclohexylmethanol 40 (4.22 g, 88%) as a pale yellow oil.

To a solution of 40 (4.06 g, 14.7 mmol) in acetone (120 mL) was added Jones reagent (8 mL, prepared by using CrO3 (2 g), H2SO4 (1.8 mL), and H2O (9mL)) at 0 °C, and the resulting mixture was stirred at 0 °C for 5.5 h. After addition of 10% aqueous Na2S2O3 solution, the solvent was evaporated. The residue was extracted with ether, and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane / ether = 8 : 1 → 3 :1) to afford 41 (2.78 g, 65%) as a colorless oil. 1H NMR analysis revealed that epimerization took place to give two diastereomers.

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Compound 41: $^1$H NMR (500 MHz, CDCl$_3$, a mixture of two diastereomers, 55 : 45) $\delta$ 0.87-0.90 (m, 0.55H), 1.13-2.08 (m, 15H), 2.59-2.62 (m, 0.45H), 3.45, 3.46 (t, $J$ = 6.3 Hz, 2H), 4.49, 4.49 (s, 2H), 7.26-7.34 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$, a mixture of two diastereomers, 55 : 45) $\delta$ 22.9, 23.8, 24.1, 25.4, 25.6, 28.0, 29.8, 29.9, 30.0, 30.5, 34.5, 37.1, 38.5, 45.1, 49.8, 70.3, 70.4, 72.9, 72.9, 127.4, 127.5, 127.6, 128.3, 138.6, 138.6, 180.8, 182.1; IR (cm$^{-1}$, CHCl$_3$) 2938, 1703, 1453, 1100; HRMS (EI+) m/z calcd for C$_{18}$H$_{26}$O$_3$: 290.18820, found 290.18865.

5-[4-(benzyloxy)butyl]-3-ethoxyspiro[3.5]nonan-1-one (42)

To a stirred solution of 41 (1.92 g, 6.61 mmol) in dichloromethane (15 mL) was added thionyl chloride (2.03 mL, 19.8 mmol) and DMF (51 $\mu$L, 0.66 mmol) at 0 °C, and the mixture was stirred at room temperature for 2 h. After evaporation of volatiles, thus-formed acid chloride was dissolved in dry acetonitrile (10 mL). To this solution was added a solution of triethylamine (1.85 mL, 13.3 mmol) in ethyl vinyl ether (20 mL) and acetonitrile (40 mL) at room temperature. The mixture was heated in a sealed tube at 150 °C for 4 days. After cooling to room temperature, water was added and the solvent was evaporated. The residue was extracted with ether, and the combined organic extracts were washed with brine, dried over anhydrous sodium sulfate, and concentrated. Most of impurities was removed by column chromatography on silica gel (hexane/ether = 10 : 1 $\rightarrow$ 5 : 1) to afford a mixture of 42 and some impurities (988 mg). This mixture was used in the next step. A part of this mixture was purified by preparative TLC (hexane/acetone) to give pure 42 as a mixture of four diastereomers (41 : 26 : 20 : 13).

Compound 42: $^1$H NMR (500 MHz, CDCl$_3$, a mixture of four diastereomers, 41 : 26 : 20 : 13) $\delta$ 1.18-1.96 (m, 18H), 2.74-3.57 (m, 6H), 3.80-4.16 (m, 1H), 4.49 (s, 2H), 7.25-7.34 (m, 5H); $^{13}$C NMR (125 MHz, CDCl$_3$, a mixture of four diastereomers) $\delta$ 15.2, 15.3, 15.3, 22.1, 22.3, 22.7, 22.8, 24.2, 24.3, 24.7, 24.8, 26.7, 27.1, 27.9, 29.5, 29.8, 29.9, 30.5, 30.9, 35.7, 38.8, 41.5, 49.8, 50.5, 50.8, 64.9, 65.2, 65.4, 69.8, 70.3, 70.3, 70.5, 70.5, 71.0, 71.7, 71.7, 71.8, 72.8, 72.9, 72.9, 74.9, 75.2, 127.4, 127.5, 127.5, 127.6, 127.6, 128.3, 128.3, 138.6, 138.6, 138.7, 212.9, 213.3; IR (cm$^{-1}$, CHCl$_3$) 2936, 1765, 1455, 1210, 1115; HRMS (EI+) m/z calcd for C$_{22}$H$_{32}$O$_3$: 344.23515, found 344.23490.
5-(but-3-enyl)-3-ethoxyspiro[3.5]nonan-1-one (8f)

A mixture of crude 42 (815 mg) and palladium on carbon (10%, 668 mg) in ethanol (40 mL) was stirred under hydrogen atmosphere (1 atm) for 3.5 h. The mixture was filtrated through Celite pad, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 3 : 1 → 1 : 1) to afford 3-ethoxy-5-(4-hydroxybutyl)spiro[3.5]nonan-1-one 43 (293 mg, 1.15 mmol, 21% yield for three steps) as a pale yellow oil.

To a refluxed suspension of 43 (293 mg, 1.15 mmol), o-nitrophenyl selenocyanate (540 mg, 2.38 mmol), and molecular sieves 4A (121 mg) in dry THF (13 mL) was added a solution of tri-n-butyl phosphine (0.57 mL, 2.31 mmol) in THF (2 mL) for 10 min, and the reaction mixture was refluxed for 15 min. After cooling to room temperature, the mixture was filtered through Celite pad, and the filtrate was concentrated. Some impurities were removed by column chromatography on silica gel (hexane/ethyl acetate = 3 : 1), and the crude product was used in the next step.

To the solution of the crude product in THF (15 mL) was added a solution of hydrogen peroxide (10%, 1.18 mL) at 0 °C, and the mixture was stirred at room temperature for 11 h. Saturated aqueous Na₂S₂O₃ solution was added, and the mixture was extracted with ether. The combined organic extracts were washed with saturated aqueous NaHCO₃ solution and brine, dried over anhydrous sodium sulfate, and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 20 : 1 → 10 : 1 → 3 : 1) to afford 8f (103.8 mg, 38% yield for two steps) as a mixture of four diastereomers (33 : 23 : 23 : 21).

Compound 8f: ¹H NMR (500 MHz, CDCl₃, a mixture of four diastereomers, 33 : 23 : 23: 21) δ 1.20-2.20 (m, 16H), 2.75-3.25 (m, 2H), 3.38-3.57 (m, 2H), 3.81-4.18 (m, 1H), 4.91-5.02 (m, 1H), 5.73-5.84 (m, 1H); ¹³C NMR (125 MHz, CDCl₃, a mixture of four diastereomers) δ 15.2, 15.3, 15.3, 15.3, 22.1, 22.3, 22.5, 22.7, 22.8, 23.3, 24.7, 26.0, 26.1, 26.2, 26.8, 27.0, 27.7, 29.1, 29.2, 29.9, 31.1, 31.6, 31.7, 31.8, 32.4, 36.3, 38.2, 40.8, 49.8, 50.4, 50.5, 50.9, 64.9, 65.2, 65.4, 65.4, 69.8, 70.3, 70.9, 71.6, 71.7, 71.8, 75.0, 75.2, 77.2, 77.2, 114.2, 114.4, 114.4, 114.8, 114.8, 138.5, 138.5, 138.9, 139.2, 212.8, 213.2, 214.1, 214.2; IR (cm⁻¹, CHCl₃) 2936, 1767, 1640, 1447, 1374, 1347, 1188, 1123, 914; HRMS (EI⁺) m/z calcd for C₁₅H₂₄O₂: 236.17763, found 236.17757.

4. $^1$H and $^{13}$C NMR spectra of new compounds
cis-1c

trans-1c
Supplementary Material (ESI) for Chemical Communications
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