Supporting information for:

Copper-catalyzed enantioselective synthesis of trans 1-alkyl-2-substituted cyclopropanes via tandem conjugate addition-intramolecular enolate trapping
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**General procedures:** Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F<sub>254</sub> silica gel plates and compounds were visualized with KMnO<sub>4</sub> reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with MgSO<sub>4</sub>. Concentration of solutions was conducted with a rotary evaporator. Progress of the reactions and conversion was determined by GC-MS (GC, HP6890; MS, HP5973) with an HPS column (Agilent Technologies, Palo Alto, CA). EE and regioselectivities were determined by chiral GC (HP6890, Chirasil-Dex-CB 25 m 0.25 mm x 0.25 μm; HP6890, Chiraldex G-TA 30 m 0.25 mm x 0.25 μm) using flame ionization detection or HPLC analysis (chiralcel OB-H, 4.6 x 250 mm, 5 μ, 40 °C, 0.5 mL/min, 210 nm; chiralcel OD-H, 4.6 x 250 mm, 5 μ, 40 °C, 0.5 mL/min, 210 nm) (in comparison to authentic samples of racemates of the products). Optical rotations were measured in CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub> on a Schimdt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). 1H NMR spectra were recorded at 400 MHz with CDCl<sub>3</sub> as solvent (Varian AMX400 spectrometer). 13C NMR spectra were obtained at 100.59 MHz in CDCl<sub>3</sub>. The nature of the carbon was determined from APT 13C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks (CHCl<sub>3</sub>, δ = 7.26 for hydrogen atoms, δ = 77.16 for carbon atoms). The following abbreviations were used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; br, broad; m, multiplet. High resolution mass spectra were determined on a FTMS Orbitrap Scientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HPS column (Agilent Technologies, Palo Alto, CA).

All reactions under a N<sub>2</sub> atmosphere were conducted using standard Schlenk techniques. CH<sub>2</sub>Cl<sub>2</sub> was distilled from CaH<sub>2</sub> under a N<sub>2</sub> atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under N<sub>2</sub> prior to use. EtO<sub>2</sub> was distilled from Na using benzophenone as indicator under a N<sub>2</sub> atmosphere prior to use. tBuOMe was distilled from CaH<sub>2</sub> under a N<sub>2</sub> atmosphere prior to use. Cui was purchased from Sigma-Aldrich. (R)-TolBINAP and (S)-TolBINAP were purchased from Sigma-Aldrich. Grignard reagents were purchased from Sigma-Aldrich (MeMgBr, EtMgBr, nBuMgBr and hexylMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et<sub>2</sub>O following standard procedures. Grignard reagents were titrated using sBuOH and catalytic amounts of 1,10-phenanthroline prior to use. 3-butenolic acid, PhSeCl, crotonic acid, DIC, DCC, EISH, OXONE<sup>®</sup>, BuOK, (E)-2-butenal diethyl acetal, DIBAL-H were purchased from Sigma-Aldrich. MeCN, DMF, nBuLi, iododecane were purchased from ACROS. MeOH was purchased from Lab-Scan. Azobis(isobutyronitrile) was purchased from Janssen Chimica. (E)-methyl 4-bromobut-2-enoate was purchased from Sigma-Aldrich and was purified by flash column chromatography (elucent 1:99 Et<sub>2</sub>O/pentane) prior to use. NCS was purchased from Sigma-Aldrich and was purified by recrystallization from AcOH prior to use. NBS was purchased from Sigma-Aldrich and was purified by recrystallization from H<sub>2</sub>O prior to use.

**Synthesis of substrates:**

**Chlorination of 3-butenolic acid:**

The procedure described in ref 11 was followed. 40 mmol scale, omitting mol sieves, 75% yield, instead of column chromatography the product was recrystallized from Et<sub>2</sub>O:pentane 1:4.

**(E)-4-chlorobut-2-enolic acid (4-chlorocrotonic acid), data in accordance with data described in ref 1.**

**Formation of the methyl ester from 4-chlorocrotonic acid:**

In a dried round-bottom two necked flask equipped with septum and stirring bar under a N<sub>2</sub> atmosphere, the substrate (1.0 equiv.) and DMAP (0.1 equiv.) were dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (5.0 mL/mmol substrate). After 5 min stirring at room temperature the mixture was cooled to 0 °C and subsequently MeOH (1.2 equiv.) and DIC (1.05 equiv.) were added. After stirring for 4 h (0 °C to room temperature) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract was dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:199 to 2:98 Et<sub>2</sub>O/pentane) yielded the product as a colorless oil.

**(E)-methyl 4-chlorobut-2-enolate (6f); data in accordance with data described in ref 3.**

[8.5 mmol scale, 51% yield (reduced yield presumably due to volatility), colorless oil]

General procedure for the formation of the thioesters from α,β-unsaturated carboxylic acids:

In a dried round-bottom two necked flask equipped with septum and stirring bar under a N<sub>2</sub> atmosphere, the substrate (1.0 equiv.) and DMAP (0.1 equiv.) were dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (1.5 mL/mmol substrate). After 5 min stirring at room temperature the mixture was cooled to 0 °C and subsequently EISH (1 equiv.) and DCC (1.05 equiv.) in CH<sub>2</sub>Cl<sub>2</sub> (0.5 mL/mmol substrate) were added. After stirring for 4 h (0 °C to room temperature) the solution was filtered over celite. The filtrate was washed with pentane and then the organic extract was dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 4:96 Et<sub>2</sub>O/pentane) yielded the product as a colorless oil with a slight impurity (5-10% of presumably trans 2-ethyl 2-(ethylthio)cyclopropanecarboxylic acid).

Further purification of (E)-S-ethyl 4-chlorobut-2-enethioate (6b):<sup>5</sup>

In a round-bottom flask equipped with septum and stirring bar, the substrate (~90% product and ~10% side product) was dissolved in a mixture of H<sub>2</sub>O and MeCN (1:4.3 3.0 mL/mmol substrate). The mixture was cooled to 0 °C and OXONE<sup>®</sup> (49% active O<sub>3</sub>, 0.1 equiv.) was added. After vigorous stirring for 20 min the reaction mixture was warmed to room temperature and vigorously stirred for another 40 min. Subsequently the reaction was quenched at 0 °C with brine (10 mL/mmol substrate) and 5. The non pure (E)-S-ethyl 4-chlorobut-2-enethioate has been used for the intramolecular 1,4-addition without any influence on the ee.
the mixture was extracted with Et₂O (3x 10 mL/mmol substrate), the combined organic extracts were dried and concentrated to a colorless oil. Flash column chromatography (gradient 1:199 to 2:98 Et₂O:pentane) yielded the product as a colorless oil.

(E)-S-ethyl 4-chlorobut-2-enethioate (6b):

[45 mmol scale, 63% yield, colorless oil]

Further purification of by ¹H NMR estimated 10 mmol scale + 0.75 mmol side product, 94% yield (9.4 mmol product), colorless oil

iodeundecane was used, 33 mmol scale, 25% yield (2 steps), off-white solid, mp: 39.6 °C.

The mixture was extracted with Et₂O (3x 3.0 mL/mmol substrate) and then the organic extracts were washed with brine (1x 3.0 mL/mmol substrate) and then Et₂O (3x 4.0 mL/mmol substrate). The organic extract were washed with brine (1x 4.0 mL/mmol substrate), dried and concentrated to a yellow oil. The product was used directly in the next step.

Thioesterification of 4-bromocrotonic acid was performed according to the general procedure for the formation of thioesters from α,β-unsaturated carboxylic acids using DCC (vide supra).

(E)-S-ethyl 4-bromobut-2-enethioate (6a) data in accordance with data described in ref 7.

Purified by flash chromatography (1:98 Et₂O:pentane).

[21 mmol scale, 70% yield, colorless oil]

General procedure for the formation of 1-chloro 2-en-4-ones:⁶

1. Synthesis of (E)-4-ethoxypentadeca-1,3-diene:

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere iBuOK (2.0 equiv.) was dissolved in anhydrous THF (1.5 mL/mmol substrate). The mixture was cooled to −78 °C and (E)-2-butenal diethyl acetal (1.0 equiv.) was added dropwise. The reaction mixture was cooled to −95 °C and nBuLi (1.6 m in hexanes, 2.0 equiv.) was added dropwise. After stirring for 2 h at room temperature the reaction mixture was treated with the iodoalkane (1 equiv.) and allowed to warm up to −40 °C slowly. Then the reaction was quenched with a mixture of water and THF (1:1, 2.0 mL/mmol substrate). The aqueous phase was extracted with Et₂O (3x 3.0 mL/mmol substrate) and then the organic extracts were washed with brine (1x 3.0 mL/mmol substrate), dried and concentrated to a yellow oil. The product was used directly in the next step.

2. Electrophilic trapping of ethoxypentadeca-1,3-diene:

In a dried roundbottom flask equipped with septum and stirring bar the substrate (1.0 equiv.) was dissolved in a mixture of water and THF (1: 1 4.0 mL/mmol substrate). The reaction mixture was cooled to 0 °C and NCS (1.05 equiv.) was added. After stirring for 16 h the reaction mixture was treated with an aq. 5% NaHCO₃ solution (1x 4.0 mL/mmol substrate) and then organic extracts were washed with brine (1x 4.0 mL/mmol substrate), dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 2:98 Et₂O:pentane) yielded the product.

(E)-1-chloropentadec-2-en-4-one (6e):

[iodoundecane was used, 33 mmol scale, 25% yield (2 steps), off-white solid, mp: 39.6 °C]

¹H NMR δ 6.80 – 6.70 (m, 1H), 6.27 (dt, J = 15.6, 1.5 Hz, 1H), 6.15 – 6.08 (m, 2H), 2.49 (t, J = 7.4 Hz, 2H), 1.60 – 1.48 (m, 2H), 1.29 – 1.09 (m, 16H). ¹³C NMR δ 199.63 (C), 139.12 (C), 131.49 (CH), 42.90 (CH₂), 40.88 (CH₂), 31.90 (CH₃), 29.60 (2x CH₂), 29.47 (CH₂), 29.33 (CH₂), 29.20 (CH₂), 23.90 (CH₂), 22.67 (CH₂), 14.09 (CH₂). Anal. Calc. for C₁₅H₂₇ClO: C, 69.61; H, 10.51; Found: C, 69.68, H, 10.65; MS m/z 223 (M⁺-Cl, 1), 222 (M⁺-Cl, 6), 95 (C₆H₇O, 49), 82 (C₅H₆O, 38), 81 (C₄H₅O, 100); HRMS calcd. for C₁₅H₂₇ClO 259.1823, found 259.1817.

(E)-1-bromopentadec-2-en-4-one (6c):

The general procedure for the formation of 1-chloro 2-en-4-ones⁶ was followed using iodoundecane, NCS was replaced by NBS. 3 h reaction time was used for the trapping, 5 mmol scale, 28 % yield (2 steps), slightly brown solid, mp: 40.9-41.2 °C

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1H NMR δ 6.82 (dt, J = 15.6, 7.3 Hz, 1H), 6.23 (dt, J = 15.6, 1.2 Hz, 2H), 4.00 (dd, J = 7.3, 1.2 Hz, 2H), 2.53 (t, J = 7.4 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.33 – 1.12 (m, 16H), 0.85 (t, J = 6.9 Hz, 3H); 13C NMR δ 199.93 (C), 139.30 (CH), 132.15 (CH), 40.84 (CH2), 31.98 (CH2), 29.83 (CH2), 29.68 (2x CH2), 29.55 (CH2), 29.49 (CH2), 29.41 (CH2), 29.29 (CH2), 24.02 (CH2), 22.77 (CH3), 14.20 (CH3). Anal. Calc. for C15H27BrClO: C, 59.40; H, 8.97; Found: C, 59.40, H, 8.90; MS m/z 327 (M+ Br)\[\text{enantiomer}\], 1003 (C15H27Br, 34), 118 (C15H27Br\[\text{enantiomer}\]), 103 (C15H27Br), 83 (C15H27O, 39); HRMS calcd. for C15H27BrClO: 327.1117, found 327.1108.

General procedure for the Cu-catalyzed 1,4-addition of Grignard reagent to 4-chlorocrotonates leading to 4-chloro 3-substituted butenoates: In a dried Schlenk tube equipped with septum and stirring bar under a N2 atmosphere, the premade catalyst solution (Cul (1 mol%); (R)-TolBINAP (1.5 mol%); in anhydrous tBuOMe (8 mL/mmol substrate)) was cooled to −78 °C and the Grignard reagent (1-3 M solution in Et2O, 1.10 or 1.15 equiv.) was added. After stirring for 10 min, a solution of the substrate (1.0 equiv.) in anhydrous CH2Cl2 (additional 2.0 mL/mmol substrate) was added over 2 h with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at −78 °C. Subsequently the reaction mixture was quenched at −78 °C with EtOH (0.4 mL/mmol substrate), followed by a 1 M aq. NH4Cl-solution (2 mL/mmol substrate) and was allowed to warm to room temperature. Then a 1 M aq. NH4Cl-solution (additional 10 mL/mmol substrate) and Et2O (10 mL/mmol substrate) were added and the layers were separated. After extraction with Et2O (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil.

General procedure for the Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to 2-substituted cyclopropanecarbothioates: In a dried Schlenk tube equipped with septum and stirring bar under a N2 atmosphere, the premade catalyst solution (Cul (1 mol%); (R)-TolBINAP (1.5 mol%); in anhydrous tBuOMe (8 mL/mmol substrate)) was cooled to −78 °C and the Grignard reagent (1-3 M solution in Et2O, 1.10 or 1.15 equiv.) was added. After stirring for 10 min, a solution of the substrate (1.0 equiv.) in anhydrous CH2Cl2 (additional 2.0 mL/mmol substrate) was added over 2 h with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at −78 °C. Subsequently the reaction mixture was quenched at −78 °C with EtOH (0.4 mL/mmol substrate), followed by a 1 M aq. NH4Cl-solution (2 mL/mmol substrate) and was allowed to warm to room temperature. Then a 1 M aq. NH4Cl-solution (additional 10 mL/mmol substrate) and Et2O (10 mL/mmol substrate) were added and the layers were separated. After extraction with Et2O (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:95 Et2O:pentane) yielded the product as a colorless oil.

General procedure for the tandem Cu-catalyzed 1,4-addition of Grignard reagent to 4-chloro-3-substituted butanoates: In a dried Schlenk tube equipped with septum and stirring bar under a N2 atmosphere, the premade catalyst solution (Cul (1 mol%); (R)-TolBINAP (1.5 mol%); in anhydrous tBuOMe (8 mL/mmol substrate)) was cooled to −78 °C and the Grignard reagent (1-3 M solution in Et2O, 1.10 or 1.15 equiv.) was added. After stirring for 10 min, a solution of the substrate (1.0 equiv.) in anhydrous CH2Cl2 (additional 2.0 mL/mmol substrate) was added over 2 h with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at −78 °C. Subsequently the reaction mixture was quenched at −78 °C with EtOH (0.4 mL/mmol substrate), followed by a 1 M aq. NH4Cl-solution (2 mL/mmol substrate) and was allowed to warm to room temperature. Then a 1 M aq. NH4Cl-solution (additional 10 mL/mmol substrate) and Et2O (10 mL/mmol substrate) were added and the layers were separated. After extraction with Et2O (2x 10 mL/mmol substrate), the combined organic extracts were dried and carefully concentrated to a yellow oil. Flash column chromatography (1:95 Et2O:pentane) yielded the product as a colorless oil.
Furthermore, 1H NOESY experiments (vide supra) performed with (1R,2R)-S-ethyl 2-methylcyclopropanecarboxylate also confirm the trans configuration.

(1R,2R)-S-ethyl 2-hexylcyclopropanecarboxylate (8b):
[1.0 mmol scale, 87% yield, 94% ee, colorless oil]

\[\text{[\(\alpha\)]}_D^{25} = -107.2 \text{ (c=1.0, CH}_2\text{Cl}_2); \text{ 1H NMR \(\delta\) 2.85 (qd, \(J = 7.4\) Hz, 1.1 Hz, 2H), 1.70 (dt, \(J = 8.5\) Hz, 4.3 Hz, 1H), 1.58 – 1.44 (m, 1H), 1.37 – 1.27 (m, 1H), 1.22 (td, \(J = 7.4\) Hz, 1.1 Hz, 3H), 1.09 (d, \(J = 6.0\) Hz, 3H).] \]

\[\text{13C NMR \(\delta\) 198.66 (C), 31.37 (CH, d, \(J = 168.4\) Hz), 23.33 (CH), t, \(J = 141.2\) Hz), 19.75 (CH, d, \(J = 169.5\) Hz), 19.14 (CH), t, \(J = 165.2\) Hz), 18.02 (CH3, q, \(J = 126.5\) Hz), 14.98 (CH3, q, \(J = 128.0\) Hz), trans product according to NOE (see other SI, also for COSY and HOSY); MS m/z 174 (M+, 7), 83 (M-SEt, 100), 55 (M-COSeT, 29); HRMS calcd. for C10H15O3 173.0880, found 173.0876; Ee was determined by chiral GC analysis of methyl 2-methylcyclopropanecarboxylate, column: Chiraladex-G-TA, 50 °C for 30 min, retention times (min): 10.4 ((R,R)-enantiomer), 11.8 ((S,S)-enantiomer).]

(1R,2R)-S-ethyl 2-ethylcyclopropanecarboxylate (8g):
[1.0 mmol scale, 56% yield (volatile product), 87% ee, colorless oil]

\[\text{[\(\alpha\)]}_D^{25} = -98.3 \text{ (c=1.0, CH}_2\text{Cl}_2); \text{ 1H NMR \(\delta\) 2.85 (qd, \(J = 7.4\) Hz, 1.1 Hz, 2H), 1.70 (dt, \(J = 8.5\) Hz, 4.3 Hz, 1H), 1.58 – 1.44 (m, 1H), 1.37 – 1.27 (m, 1H), 1.22 (td, \(J = 7.4\) Hz, 1.1 Hz, 3H), 1.09 (d, \(J = 6.0\) Hz, 3H).] \]

\[\text{13C NMR \(\delta\) 198.66 (C), 31.37 (CH, d, \(J = 168.4\) Hz), 23.33 (CH), t, \(J = 141.2\) Hz), 19.75 (CH, d, \(J = 169.5\) Hz), 19.14 (CH), t, \(J = 165.2\) Hz), 18.02 (CH3, q, \(J = 126.5\) Hz), 14.98 (CH3, q, \(J = 128.0\) Hz), trans product according to NOE (see other SI, also for COSY and HOSY); MS m/z 174 (M+, 7), 83 (M-SEt, 100), 55 (M-COSeT, 29); HRMS calcd. for C10H15O3 173.0880, found 173.0876; Ee was determined by chiral GC analysis of methyl 2-methylcyclopropanecarboxylate, column: Chiraladex-G-TA, 50 °C for 30 min, retention times (min): 10.4 ((R,R)-enantiomer), 11.8 ((S,S)-enantiomer).]

(1R,2R)-S-ethyl 2-ethylcyclopropanecarboxylate (8h):
[1.0 mmol scale, 67% yield, 95% ee, colorless oil]

\[\text{[\(\alpha\)]}_D^{25} = -100.1 \text{ (c=1.0, CH}_2\text{Cl}_2); \text{ 1H NMR \(\delta\) 2.85 (qd, \(J = 7.4\) Hz, 1.5 Hz, 2H), 1.78 – 1.69 (m, 1H), 1.53 – 1.42 (m, 1H), 1.37 – 1.15 (m, 6H), 0.95 (t, \(J = 7.3\) Hz, 3H), 0.77 (ddd, \(J = 8.0\) Hz, 6.5 Hz, 4.1 Hz, 1H).] \]

\[\text{13C NMR \(\delta\) 198.76 (C), 30.10 (CH), 27.16 (CH), 26.32 (CH), 23.32 (CH2), 17.71 (CH), 14.95 (CH3), 13.21 (CH); MS m/z 158 (M+, 8), 97 (M-SEt, 100), 55 (C2H5, 92); HRMS calcd. for C6H11O2 159.0835, found 159.0835; Ee was determined by chiral GC analysis of methyl 2-ethylcyclopropanecarboxylate, column: Chiraladex-G-TA, 50 °C for 30 min, 50 °C to 140 °C in 18 min, retention times (min): 41.0 ((S,S)-enantiomer), 41.6 ((R,R)-enantiomer).]

(1R,2R)-S-ethyl 2-isopropylcyclopropanecarboxylate (8i):
[1.0 mmol scale, 89% yield, 70% ee, colorless oil]

\[\text{[\(\alpha\)]}_D^{25} = -77.4 \text{ (c=1.0, CH}_2\text{Cl}_2); \text{ 1H NMR \(\delta\) 2.92 – 2.76 (m, 2H), 1.75 (dt, \(J = 8.4\) Hz, 4.3 Hz, 1H), 1.36 – 1.24 (m, 2H), 1.24 – 1.17 (m, 3H), 1.09 – 0.98 (m, 1H), 0.98 – 0.91 (m, 6H), 0.76 (ddd, \(J = 6.2\) Hz, 4.7 Hz, 2.1 Hz, 1H).] \]

\[\text{13C NMR \(\delta\) 198.65 (C), 33.20 (CH), 32.36 (CH), 29.48 (CH), 23.28 (CH), 21.81 (CH), 21.57 (CH), 16.84 (CH3), 14.91 (CH3); MS m/z 172 (M+, 4), 111 (M-SEt, 57), 69 (C2H5, 49), 55 (C2H7, 100); HRMS calcd. for C8H16O2 173.0989, found 173.0992; Ee was determined by chiral GC analysis of methyl 2-isopropylcyclopropanecarboxylate, column: Chiraladex-G-TA, 80 °C for 50 min, retention times (min): 10.4 ((R,R)-enantiomer), 11.8 ((S,S)-enantiomer).]

(1R,2R)-S-ethyl 2-isobutylcyclopropanecarboxylate (8j):
[1.0 mmol scale, 91% yield, 84% ee, colorless oil]

\[\text{[\(\alpha\)]}_D^{25} = -114.0 \text{ (c=1.0, CH}_2\text{Cl}_2); \text{ 1H NMR \(\delta\) 2.84 (qd, \(J = 7.4\) Hz, 1.4 Hz, 2H), 1.75 – 1.59 (m, 2H), 1.53 – 1.41 (m, 1H), 1.36 – 1.28 (m, 1H), 1.25 – 1.13 (m, 5H), 0.94 – 0.85 (m, 6H), 0.73 (ddd, \(J = 7.9\) Hz, 6.5 Hz, 4.0 Hz, 1H); 13C NMR \(\delta\) 198.63 (C), 42.35 (CH3), 30.43 (CH), 28.52 (CH), 23.96 (CH), 23.30 (CH2), 22.58 (CH2), 22.51 (CH2), 17.87 (CH3), 14.94 (CH3); MS m/z 186 (M+, 1), 125 (M-SEt, 92), 87 (M-COSeT, 29), 55 (C2H5, 100); HRMS calcd. for C9H17O2 187.1151, found 187.1148; Ee was determined by chiral GC analysis of methyl 2-isobutylcyclopropanecarboxylate, column: Chiraladex-G-TA, 70 °C for 50 min, retention times (min): 12.8 ((R,R)-enantiomer), 14.4 ((S,S)-enantiomer).]
(1R,2R)-S-ethyl 2-(but-3-enyl)cyclopropane carbothioate: [3.0 mmol scale, 88% yield, 94% ee, colorless oil (8k)]

$\text{[\phi]}_{D}^{20} = -111.9 (c=1.0, \text{CH}_2\text{Cl}_2); ^{1}\text{H NMR} \delta 5.88 - 5.46 (m, 1H), 5.08 - 4.64 (m, 2H), 2.76 (qd, J = 7.4 Hz, 1H), 2.25 - 1.84 (m, 2H), 1.78 - 1.55 (m, 1H), 1.40 (dd, d, J = 13.5 Hz, 8.1 Hz, 3.8 Hz, 2.0 Hz, 1H), 1.37 - 1.27 (m, 2H), 1.23 (dd, d, J = 6.0 Hz, 4.5 Hz, 1H), 1.72 (m, 1H), 1.18 - 1.07 (m, 3H), 0.74 - 0.63 (m, 1H); $^{13}\text{C NMR} \delta 197.84 (C), 137.57 (CH), 114.91 (CH), 33.10 (CH2), 32.40 (CH2), 29.94 (CH), 24.66 (CH), 23.03 (CH2), 17.42 (CH2), 14.77 (CH2); MS m/z 184 (M+ 2, 123 (M+S-SEt, 100), 95 (M-COS, 84), 55 (C3H7), 79); HRMS calcd. for C_{6}H_{10}O_{2}S 185.0995, found 185.0991; $Ee$ was determined by chiral GC analysis of methyl 2-(but-3-ethyl)cyclopropane carboxylate,\textsuperscript{11} column: Chiraladex-G-TA, 70 °C for 50 min, retention times (min): 17.4 ((R,R)-enantomer), 19.8 ((S,S)-enantomer).

(1R,2R)-S-ethyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate (8i): [0.5 mmol scale, >95% conversion, 96% ee, colorless oil]

$\text{[\phi]}_{D}^{20} = -80.0 (c=1.0, \text{value corrected for presence of Grignard dimer (1,2-di-tert-butoxyoctane), CH}_2\text{Cl}_2); ^{1}\text{H NMR} \delta 5.35 - 3.25 (m, 2H), 2.85 (qd, J = 7.4 Hz, 2.1 Hz, 2H), 1.77 - 1.69 (m, 1H), 1.57 - 1.37 (m, 5H), 1.37 - 1.25 (m, 6H), 1.18 (s, 9H), 0.76 (ddd, J = 7.9, 6.6, 4.1 Hz, 1H). Residual peaks Grignard dimer 3.35 - 3.25 (m, 4H), 1.57 - 1.37 (m, 4H), 1.37 - 1.25 (m, 4H), 1.22 (t, J = 7.4 Hz, 4H), 1.16 (s, 18H); $^{13}\text{C NMR} \delta 198.72 (C), 72.54 (CH), 61.48 (CH2), 33.13 (CH3), 30.39 (CH3), 30.31 (CH), 27.67 (CH2), 25.86 (CH2), 25.46 (CH3), 17.92 (CH3), 14.95 (CH3); Residual peaks Grignard dimer 72.46 (CH), 61.72 (CH2), 30.81 (CH3), 29.61 (CH2), 27.68 (CH2), 26.32 (CH3); MS m/z 258 (M+, 1), 141 (M-S-SEt-bu2, 72), 95 (C6H11, 100), 57 (C5H9O, 71); HRMS calcd. for C_{18}H_{32}O_{2}S 281.1546, found 281.1534; $Ee$ was determined by chiral GC analysis of methyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate,\textsuperscript{11} column Chiraladex-G-TA, 70 °C for 50 min, 70 °C to 120 °C in 100 min; retention times (min): 120.1 (1R,2R-enantomer), 121.0 (1S,2S-enantomer).

(1R,2R)-methyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate: [0.5 mmol scale, yield over 2 steps: 27% yield (extensive chromatography in attempts to separate the dimer and (1R,2R)-S-ethyl 2-(3-tert-butoxypropyl)cyclopropanecarbothioate (8i)) before the derivatization of the thioester to the methyl ester explain this low yield], 96% ee, colorless oil

(1R,2R)-S-ethyl 2-phenethylcyclopropanecarbothioate (8m): [1.0 mmol scale, 97% yield, 84% ee, colorless oil]

$\text{[\phi]}_{D}^{20} = -101.7 (c=1.0, \text{CH}_2\text{Cl}_2); ^{1}\text{H NMR} \delta 5.36 - 7.28 (m, 2H), 7.27 - 7.18 (m, 3H), 2.92 (q, J = 7.5 Hz, 2H), 2.75 (t, J = 7.5 Hz, 2H), 1.81 (dt, J = 8.3 Hz, 4.2 Hz, 2H), 1.75 - 1.53 (m, 3H), 1.39 (dt, J = 8.6 Hz, 4.3 Hz, 1H), 1.29 (t, J = 7.4 Hz, 3H), 0.82 (ddd, J = 8.0, 6.3, 4.1 Hz, 1H); $^{13}\text{C NMR} \delta 198.39 (C), 141.53 (C), 128.43 (CH), 128.40 (CH), 125.92 (CH), 35.38 (CH3), 35.04 (CH3), 30.20 (CH), 29.49 (CH2), 23.10 (CH2), 20.14 (CH), 15.76 (CH3); MS m/z 213 (M,E-CH3, 142 (C5H10O, 28), 95 (C6H9O, 100), 57 (C6H12, 62); HRMS calcd. for C_{13}H_{22}O_{2}S 251.1618, found 251.1614; $Ee$ was determined by chiral GC analysis, column Chiraladex-G-TA, 70 °C for 50 min, 70 °C to 120 °C in 100 min; retention times (min): 120.1 (1R,2R-enantomer), 121.0 (1S,2S-enantomer).

(S)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate (vide supra),\textsuperscript{11} column: chiralcel OB-H, (99:1 heptane:PrOH); retention times (min): 26.0 (S-enantomer (corresponds with the 1R,2R-enantomer)), 32.7 (R-enantomer (corresponds with the 1S,2S-enantomer)).

(5)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate was prepared via the general procedure for the Cu-catalyzed 1,4-addition of Grignard reagent to 4-chlorocrotonates leading to 4-chloro 3-substituted butenoates: [0.25 mmol scale, 89% yield, 84% ee, colorless oil]
(1R,2R)-S-ethyl 2-phenylcyclopropanecarbothioate (8n):

\[
\text{Ph} \quad \text{SEt}
\]

\[\alpha\] D = -125.0 (c=2.1, CH2Cl2); \(^1^H\) NMR \(\delta\) 7.33 – 7.18 (m, 3H), 7.14 – 7.07 (m, 2H), 2.94 (qd, \(J = 7.4\) Hz, 0.8 Hz, 2H), 2.66 (ddd, \(J = 9.2\) Hz, 6.7 Hz, 4.1 Hz, 1H), 2.26 (ddd, \(J = 8.2\) Hz, 5.2 Hz, 4.1 Hz, 1H), 1.77 (ddd, \(J = 9.3\) Hz, 5.2 Hz, 4.6 Hz, 1H), 1.59 (s, 1H), 1.42 (ddd, \(J = 8.2\) Hz, 6.7 Hz, 4.5 Hz, 1H), 1.28 (t, \(J = 7.4\) Hz, 3H); \(^1^C\) NMR \(\delta\) 197.70 (C), 140.00 (C), 126.63 (CH), 126.74 (CH), 126.32 (CH), 33.86 (CH), 28.48 (CH), 23.60 (CH), 18.87 (CH2), 14.94 (CH3); MS m/z 206 (M\(^+\), 18), 151 (C5H6OS, 65), 145 (M\(^+\)-SEt, 79), 127 (C5H7OS, 79), 117 (M\(^+\)-C=SEt, 100), 115 (C4H7OS, 93); HRMS calcd. for C23H37O 329.2839, found 329.2816; Ee was determined by chiral HPLC analysis, column: chiralcel OJ, (99:1 heptane:\text{PrOH}); retention times (min): 7.1 (major enantiomer), 9.0 (minor enantiomer).

(1R,2R)-methyl 2-phenylcyclopropanecarboxylate (8f):

\[
\text{Ph} \quad \text{OMe}
\]

\[\alpha\] D = -82.8 (c=1.0, CH2Cl2); \(^1^H\) NMR \(\delta\) 7.34 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 3.69 (s, 3H), 2.80 – 2.71 (m, 2H), 1.65 (dd, \(J = 15.1\) Hz, 7.3 Hz, 2H), 1.50 – 1.36 (m, 2H), 1.25 – 1.17 (m, 1H), 0.73 (ddd, \(J = 8.1\) Hz, 6.4 Hz, 4.2 Hz, 1H); \(^1^C\) NMR \(\delta\) 174.78 (C), 141.68 (C), 128.44 (CH), 128.38 (CH), 125.91 (CH), 51.62 (CH), 35.50 (CH), 35.04 (CH), 22.62 (CH2), 20.12 (CH2), 15.51 (CH3); MS m/z 173 (M\(^+\)-OME, 1), 130 (C7H15O, 84), 117 (C7H8, 28), 105 (C6H10, 35), 91 (C1H10, 100); HRMS calcd. for C10H12O, 205.1223, found 205.1223; Ee was determined by chiral GC analysis, column: Chiralsil-Dex-CB, 50 °C to 140 °C in 9 min, 140 °C for 50 min, 140 °C to 160 °C in 10 min; retention times (min): 24.7 (1R,2R-addition product), 25.3 (1S,2S)-enantiomer).

1-((1R,2R)-2-methylcyclopropyl)dodecan-1-one (8o):

\[
\text{Me} \quad \text{CH}_{13}
\]

\[\alpha\] D = -70.1 (c=1.0, CH2Cl2); \(^1^H\) NMR \(\delta\) 2.46 (t, \(J = 7.5\) Hz, 2H), 1.59 (ddd, \(J = 23.6\) Hz, 11.1 Hz, 5.6 Hz, 3H), 1.37 – 1.15 (m, 17H), 1.06 (d, \(J = 6.0\) Hz, 3H), 0.84 (t, \(J = 6.8\) Hz, 3H), 0.64 (ddd, \(J = 7.8\) Hz, 6.4 Hz, 3.5 Hz, 1H); \(^1^C\) NMR \(\delta\) 210.62 (C), 43.74 (CH3), 31.99 (CH3), 29.69 (2x CH3), 29.57 (CH3), 29.54 (CH3), 29.51 (CH3), 29.41 (CH3), 29.36 (CH3), 24.18 (CH3), 22.75 (CH3), 19.87 (CH3), 19.12 (CH3), 18.17 (CH3), 14.16 (CH3); MS m/z 238 (M\(^+\), 2), 111 (C7H15O, 15), 98 (C6H10O, 100), 83 (C5H7O, 15), 55 (C4H7, 27); HRMS calcd. for C10H12O, 239.2369, found 239.2351; Ee was determined by chiral GC analysis, column: ChiralSIL-DSX-CB, 50 °C to 140 °C in 9 min, 140 °C for 50 min, 140 °C to 160 °C in 10 min; retention times (min): 62.9 (1R,R-enantiomer), 64.4 (1S,S-enantiomer).

1-((1R,2R)-2-phenylcyclopropyl)dodecan-1-one (8e):

\[
\text{Ph} \quad \text{CH}_{13}
\]

\[\alpha\] D = -73.8 (c=1.0, CH2Cl2); \(^1^H\) NMR \(\delta\) 7.34 – 7.26 (m, 2H), 7.25 – 7.16 (m, 3H), 2.83 – 2.63 (m, 3H), 2.48 – 2.38 (m, 2H), 1.74 (ddd, \(J = 14.4\) Hz, 10.3 Hz, 4.1 Hz, 1H), 1.67 – 1.52 (m, 4H), 1.49 – 1.20 (m, 17H), 0.93 (t, \(J = 6.8\) Hz, 3H), 0.72 (ddd, \(J = 7.8\) Hz, 6.4 Hz, 3.7 Hz, 1H); \(^1^C\) NMR \(\delta\) 210.46 (C), 141.70 (C), 128.46 (CH), 128.40 (CH), 125.91 (CH), 43.60 (CH3), 35.65 (CH3), 35.18 (CH3), 31.99 (CH3), 29.71 (CH3), 29.70 (CH3), 29.58 (CH3), 29.52 (CH3), 29.43 (CH3), 29.36 (CH3), 28.50 (CH3), 25.19 (CH2), 24.10 (CH3), 22.77 (CH3), 17.53 (CH3), 14.20 (CH3); MS m/z 328 (M\(^+\), 1), 130 (C7H15O, 100), 91 (C6H7, 25); HRMS calcd. for C10H12O, 239.2389, found 239.2386; Ee was determined by chiral HPLC analysis, column: chiralcel OJ-H, (99:1 heptane:\text{PrOH}); retention times (min): 12.1 (1R,2R-addition product), 13.3 (1S,2S)-enantiomer.)
Formal syntheses of cascarillic acid: synthesis of (1R,2R)-2-hexylcyclopropancarbaldehyde

SI Scheme 1. Formal syntheses of cascarillic acid and grenadamide.*

\[ \text{6b} \xrightarrow{\text{Table 2}} \text{8b}, R = \text{hexyl} \]
\[ \text{R = hexyl, 83%} \]
\[ \text{9b, R = hexyl, 83%} \]
\[ \text{8p, R = heptyl, 84%, 95% ee} \]
\[ \text{9p, R = heptyl, 86%} \]

*Conditions: 8: See Table 2; 9: DIBAL-H (1.0 M solution in CH\(_2\)Cl\(_2\), 1.2 equiv.) in CH\(_2\)Cl\(_2\) (0.4 M), \(-78^\circ\text{C}, 3\text{ h.}\)

General procedure for the reduction of the thioester to an aldehyde:
In a dried Schlenk tube equipped with septum and stirring bar under a \(\text{N}_2\) atmosphere the thioester (1.0 equiv.) was dissolved in anhydrous CH\(_2\)Cl\(_2\) (2.5 mL/mmol substrate). After 5 min stirring at room temperature the mixture was cooled to \(-78^\circ\text{C}\) and DIBAL-H (1.2 equiv.) was added drop-wise. The reaction mixture was stirred for 3 h at \(-78^\circ\text{C}\). Subsequently the reaction mixture was poured into a roundbottom flask with aq. Rochelle’s salt-solution (saturated, 5 mL/mmol substrate), stirred for 1 h at \text{rt} and the layers were separated. After extraction with CH\(_2\)Cl\(_2\) (2x 5 mL/mmol substrate), the combined organic extracts were washed with the aq. Rochelle’s salt solution (2x 5 mL/mmol substrate), dried and carefully concentrated. Flash column chromatography (5:95 Et\(_2\)O:pentane) yielded the pure product.

(1R,2R)-2-hexylcyclopropancarbaldehyde (9b):
[0.5 mmol scale, 83% yield, colorless oil]

\[ \alpha^D_{20} = -36.9 \text{ (c=1.0, CH}_2\text{Cl}_2\text{), Literature value:}^{12} \alpha^D_{20} = -26.0 \text{ (c=0.35, CH}_2\text{Cl}_2\text{) for the (1R,2R)-enantiomer.} \]

Experimental data in accordance with data reported in ref 12.

Formal synthesis of grenadamide (8p): synthesis of (1R,2R)-2-heptylcyclopropancarbaldehyde
(1R,2R)-S-ethyl 2-heptylcyclopropanecarbothioate was prepared according to the general procedure for the tandem Cu-catalyzed 1,4-addition -intramolecular trapping reaction of Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates.

[1.0 mmol scale, 84% yield, 95% ee, colorless oil]

\[ \alpha^D_{20} = -107.9 \text{ (c=1.0, CH}_2\text{Cl}_2\text{), ^1H NMR 5.2.84 (qd, J = 7.4 Hz, 1.0 Hz, 2H), 1.71 (dt, J = 8.2 Hz, 4.3 Hz, 1H), 1.54 – 1.14 (m, 17H), 0.84 (t, J = 6.8 Hz, 3H), 0.74 (ddd, J = 7.9 Hz, 6.6 Hz, 4.0 Hz, 1H); ^13C NMR 5 198.59 (C), 33.20 (CH\(_2\)), 31.90 (CH\(_2\)), 30.32 (CH), 29.31 (CH\(_2\)), 29.29 (CH\(_2\)), 29.08 (CH\(_2\)), 25.51 (CH\(_2\)), 23.28 (CH\(_2\)), 22.72 (CH\(_2\)), 17.81 (CH\(_2\)), 14.93 (CH\(_2\)), 14.15 (CH\(_2\)). MS m/z 228 (M\(^+\), 1), 167 (M\(^+\)-SET, 92), 69 (C\(_7\)H\(_4\)), 55 (C\(_4\)H\(_9\)), 38, 35 (C\(_3\)H\(_5\)), 93; HRMS calcd. for C\(_{13}\)H\(_{25}\)O\(_2\) 229.1621, found 229.1618; \(\text{Ee was determined by chiral GC analysis for methyl 2-heptylcyclopropanoate,}^{11} \text{ column: Chiralox-G-TA, 85 °C for 50 min, 85 °C to 180 °C in 9.5 min, retention times (min): 53.0 ((R,R)-enantiomer), 53.6 ((S,S)-enantiomer).} \]

(1R,2R)-2-heptylcyclopropancarbaldehyde (9p) was prepared according to the general procedure for the reduction of the thioester to an aldehyde.
[0.5 mmol scale, 84% yield, colorless oil]

\[ \alpha^D_{20} = -43.9 \text{ (c=1.0, CHCl}_3\text{), Literature value:}^{13} \alpha^D_{20} = +41.4 \text{ (c=1.45, CHCl}_3\text{) for the trans (1S,2S)-enantiomer.} \]

Experimental data in accordance with data reported in ref 13.

(E)-S-ethyl 4-chlorobut-2-enethioate (6b):
(E)-1-chloropentadec-2-en-4-one (6e):
(E)-1-bromopentadec-2-en-4-one (6e):
(S)-S-ethyl 3-(chloromethyl)nonanethioate (7b):
racemic methyl 3-(chloromethyl)nonanoate:

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(S)-3-(chloromethyl)-1-phenylhexadecan-5-one (7e):
(1R,2R)-S-ethyl 2-hexylcyclopropanecarbothioate (8b):
racemic methyl 2-hexylcyclopropanecarboxylate:

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(1R,2R)-methyl 2-hexylcyclopropanecarboxylate:

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(1R,2R)-S-ethyl 2-methylcyclopropanecarbothioate (8g): spectra contain traces of (S)-S-ethyl 4-chloro-3-methylbutanethioate and Et₂O.
Coupled $^{13}$C

HQSC
For the trans-cyclopropane a coupling of H(0.7 ppm) and H(1.7 ppm) is expected and a coupling of H(1.3 ppm) and H(1.5 ppm).
For the cis-cyclopropane a couplings of H(0.7 ppm), H(1.5 ppm) and H(1.7 ppm) are expected.
Since the coupling of H(1.5 ppm) and H(1.7 ppm) is absent it is concluded that the cyclopropane is in the trans configuration.
racemic methyl 2-methylcyclopropanecarboate:

(1R,2R)-methyl 2-methylcyclopropanecarboate:
(1R,2R)-S-ethyl 2-ethylcyclopropanecarbothioate (8h): spectra contain traces of (S)-S-ethyl 3-(chloromethyl)pentanethioate and Et₂O
racemic methyl 2-ethylcyclopropanecarboxylate:

(1R,2R)-methyl 2-ethylcyclopropanecarboxylate:
(1R,2R)-S-ethyl 2-isopropylcyclopropanecarbothioate (8i): spectra contain traces of (R)-S-ethyl 3-(chloromethyl)-4-methylpentanethioate.
racemic methyl 2-isopropylcyclopropanecarboxylate:

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(1R,2R)-methyl 2-isopropylcyclopropanecarboxylate:

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(1R,2R)-S-ethyl 2-isobutylcyclopropanecarbothioate (8j):
racemic methyl 2-isobutylcyclopropanecarboxylate:

(1R,2R)-methyl 2-isobutylcyclopropanecarboxylate:
(1R,2R)-S-ethyl 2-(but-3-enyl)cyclopropanecarbothioate (8k):
**racemic methyl 2-(but-3-enyl)cyclopropanecarboxylate:**

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**(1R,2R)-methyl 2-(but-3-enyl)cyclopropanecarboxylate:**

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(1R,2R)-S-ethyl 2-(3-tert-butoxypropyl)cyclopropanecarbothioate (8i): spectra contain ~1.1 equivalent of Grignard dimer (1,8-di-tert-butoxyoctane) mainly formed in the preparation of the Grignard reagent.
Racemic methyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate:

(1R,2R)-methyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate:
(1R,2R)-methyl 2-(3-tert-butoxypropyl)cyclopropanecarboxylate: spectra contain traces of EtOAc and H₂O.
(1R,2R)-methyl 2-phenethylcyclopropanecarbothioate (8m): spectra contain traces of (S)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate
racemic *trans* 2-phenethylcyclopropanecarboxylate:

\[
\text{Chromatogram}
\]

<table>
<thead>
<tr>
<th>Pk #</th>
<th>Name</th>
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<th>Area</th>
<th>Area Percent</th>
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<tbody>
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</table>

**Totals**

45285300 100.000

(1R,2R)-methyl 2-phenethylcyclopropanecarboxylate: see also (S)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate

\[
\text{Chromatogram}
\]

<table>
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<tr>
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**Totals**

6738548 100.000
(S)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate: spectra contain traces of (1R,2R)-S-ethyl 2-phenethylcyclopropanecarbothioate
(1R,2R)-S-ethyl 2-phenylcyclopropanecarbothioate (8n): spectra contain traces of CH₂Cl₂ and H₂O
Racemic trans S-ethyl 2-phenylcyclopropanecarbothioate:

1: 230 nm, 8 nm

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Enantioenriched trans S-ethyl 2-phenylcyclopropanecarbothioate:

1: 230 nm, 8 nm

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1-((1R,2R)-2-phenethylcyclopropyl)dodecan-1-one (8e): spectra contain traces of (S)-3-(chloromethyl)-1-phenylhexadecan-5-one
racemic trans 1-((1R,2R)-2-phenethylcyclopropyl)dodecan-1-one:

1-((1R,2R)-2-phenethylcyclopropyl)dodecan-1-one:
1-((1R,2R)-2-methylcyclopropyl)dodecan-1-one (8o): spectra contain traces of (S)-1-chloro-2-methylpentadecan-4-one
racemic trans 1-(2-methylcyclopropyl)dodecan-1-one:

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1-((1R,2R)-2-methylcyclopropyl)dodecan-1-one:

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(1R,2R)-methyl 2-phenethylcyclopropanecarboxylate (8f): spectra contain traces of (S)-methyl 3-(chloromethyl)-5-phenylpentanoate
racemic trans methyl 2-phenethylcyclopropanecarboxylate:

(1R,2R)-methyl 2-phenethylcyclopropanecarboxylate:
(1R,2R)-S-ethyl 2-heptylcyclopropanecarbothioate (8p):
racemic methyl 2-heptylcyclopropanoate:

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(1R,2R)-methyl 2-heptylcyclopropanoate:

<table>
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