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Published in:
Journal of the American Chemical Society

DOI:
[10.1021/ja105704m](https://doi.org/10.1021/ja105704m)

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
2010

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Den Hartog, T., Rudolph, A., Macia, B., Minnaard, A. J., & Feringa, B. L. (2010). Copper-catalyzed enantioselective synthesis of trans-1-Alkyl-2-substituted cyclopropanes via tandem conjugate addition-intramolecular enolate trapping. *Journal of the American Chemical Society*, 132(41), 14349 - 14351. <https://doi.org/10.1021/ja105704m>

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Supporting information for:

Copper-catalyzed enantioselective synthesis of *trans* 1-alkyl-2-substituted cyclopropanes via tandem conjugate addition-intramolecular enolate trapping

Tim den Hartog, , Alena Rudolph, Beatriz Maciá, Adriaan J. Minnaard,* and Ben L. Feringa*

General procedures: Thin-layer chromatography (TLC) was performed on commercial Kieselgel 60 F₂₅₄ silica gel plates and compounds were visualized with KMnO₄ reagent. Flash chromatography was performed on silica gel. Drying of solutions was performed with MgSO₄. 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 HP5 column (Agilent Technologies, Palo Alto, CA). *Ee* and regioselectivities were determined by chiral GC (HP6890, Chiralsil DEX-CB 25 m x 0.25 mm x 0.25 µm; HP6890, Chiraldex G-TA 30 m x 0.25 mm x 0.25 µm) using flame ionization detection or HPLC analysis (chiralcel OB-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm; chiralcel OJ-H, 4.6 x 250 mm, 5 m, 40 °C, 0.5 mL/min, 210 nm) (in comparison to authentic samples of racemates of the products). Optical rotations were measured in CH₂Cl₂ or CHCl₃ on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). ¹H NMR spectra were recorded at 400 MHz with CDCl₃ as solvent (Varian AMX400 spectrometer). ¹³C NMR spectra were obtained at 100.59 MHz in CDCl₃. The nature of the carbon was determined from APT ¹³C NMR experiments. Chemical shifts were determined relative to the residual solvent peaks (CHCl₃, 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 Fischer Scientific mass spectrometer by ESI measurements in positive mode. Fragmentation patterns were determined by GC-MS (GC, HP6890; MS, HP5973) with an HP5 column (Agilent Technologies, Palo Alto, CA).

All reactions under a N₂ atmosphere were conducted using standard Schlenk techniques. CH₂Cl₂ was distilled from CaH₂ under a N₂ atmosphere prior to use. THF was distilled from Na using benzophenone as indicator under N₂ prior to use. Et₂O was distilled from Na using benzophenone as indicator under a N₂ atmosphere prior to use. *t*BuOMe was distilled from CaH₂ under a N₂ 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, *i*BuMgBr and hexylMgBr) or prepared from the corresponding alkyl bromides and magnesium turnings in anhydrous Et₂O following standard procedures. Grignard reagents were titrated using *s*BuOH and catalytic amounts of 1,10-phenanthroline before use.

3-butenic acid, PhSeCl, crotonic acid, DIC, DCC, EtSH, OXONE[®], *t*BuOK, (*E*)-2-butenal diethyl acetal, DIBAL-H were purchased from Sigma-Aldrich. MeCN, DMAP, *n*BuLi, iodoundecane 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 (eluent 1:99 Et₂O: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 H₂O prior to use.

Synthesis of substrates:

Chlorination of 3-butenic acid:¹

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 Et₂O:pentane 1:4.

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

Formation of the methyl ester from 4-chlorocrotonic acid:²

In a dried roundbottom two necked flask equipped with septum and stirring bar under a N₂ atmosphere, the substrate (1.0 equiv.) and DMAP (0.1 equiv.) were dissolved in anhydrous CH₂Cl₂ (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 were dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:199 to 2:98 Et₂O:pentane) yielded the product as a colorless oil.

(*E*)-methyl 4-chlorobut-2-enoate (**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 thioesters from α,β-unsaturated carboxylic acids:

In a dried roundbottom two necked flask equipped with septum and stirring bar under a N₂ atmosphere, the substrate (1.0 equiv.) and DMAP (0.1 equiv.) were dissolved in anhydrous CH₂Cl₂ (1.5 mL/mmol substrate). After 5 min stirring at room temperature the mixture was cooled to 0 °C and subsequently EtSH (1 equiv.) and DCC (1.05 equiv.) in CH₂Cl₂ (0.5 mL/mmol substrate)⁴ 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 were dried and concentrated to a yellow oil. Flash column chromatography (gradient 1:99 to 4:96 Et₂O:pentane) yielded the product as a colorless oil with a slight impurity (5-10% of presumably trans *S*-ethyl 2-(ethylthio)cyclopropanecarbothioate).

Further purification of (*E*)-*S*-ethyl 4-chlorobut-2-enethioate (**6b**):⁵

In a roundbottom flask equipped with septum and stirring bar, the substrate (~90% product and ~10% side product) was dissolved in a mixture of H₂O and MeCN (1:4 3.0 mL/mmol substrate). The mixture was cooled to 0 °C and OXONE[®] (49% active O₂, 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

¹ J. A. Tunge, S. R. Mellegaard, *Org. Lett.* **2004**, 6, 1205-1207.

² T. Aoyama, S. Teasawa, K. Sudo, T. Chioiri, *Chem. Pharm. Bull.* **1984**, 32, 3759-3760.

³ C. Schmidt, U. Kazmaier, *Eur. J. Org. Chem.* **2008**, 887-894.

⁴ Alternatively DIC (1.05 equiv.) was used with comparable results.

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]

¹H NMR δ 6.81 (dt, *J* 15.1 Hz, 6.0 Hz, 1 H), 6.29 (dd, *J* = 15.2 Hz, 1.4 Hz, 1 H), 4.11 (d, *J* = 6.0 Hz, 2 H), 2.90 (q, *J* = 7.4 Hz, 2 H), 1.22 (t, *J* = 7.4 Hz, 3 H); ¹³C NMR δ 189.36 (C), 137.31 (CH), 130.52 (CH), 42.65 (CH₂), 23.48 (CH₂), 14.73 (CH₃); MS *m/z* 166 (M⁺[Cl³⁷], 2), 164 (M⁺[Cl³⁵], 6), 105 (M⁺[Cl³⁷]-SEt, 33), 103 (M⁺[Cl³⁵]-SEt, 100), 75 (M⁺[Cl³⁵]-COSEt, 20); HRMS calcd. for C₆H₁₀ClOS 165.0135, found 165.0132.

Bromination of crotonic acid was performed according to ref 6.

(*E*)-4-bromobut-2-enoic acid (4-bromocrotonic acid) data in accordance with data described in ref 6.

[230 mmol scale, 70% yield, white solid, mp: 74.7-75.3 °C].

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 (1:99 Et₂O:pentane).

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

General procedure for the formation of 1-chloro 2-en-4-ones:⁸

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

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere *t*BuOK (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 *n*BuLi (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 extracted with 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. 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), 4.15 – 4.08 (m, 2H), 2.49 (t, *J* = 7.4 Hz, 2H), 1.60 – 1.48 (m, 2H), 1.29 – 1.09 (m, 16H), 0.81 (t, *J* = 6.8 Hz, 3H); ¹³C NMR δ 199.63 (C), 139.12 (CH), 131.49 (CH), 42.90 (CH₂), 40.88 (CH₂), 31.90 (CH₂), 29.60 (2x CH₂), 29.47 (CH₂), 29.41 (CH₂), 29.33 (CH₂), 29.20 (CH₂), 23.90 (CH₂), 22.67 (CH₂), 14.09 (CH₃); 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 (C₅H₅O, 100); HRMS calcd. for C₁₅H₂₆ClO 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-ones⁸ 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]

⁶ T. den Hartog, B. Maciá, A. J. Minnaard, B. L. Feringa, *Adv. Synth. Catal.* **2010**, 352, 999-1013.

⁷ A. W. van Zijl, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2008**, 73, 5651–5653.

⁸ A. Deagostino, P. B. Tivola, C. Prandi, P. Venturello, *Synlett* **1999**, 1841-1843.

^1H NMR δ 6.82 (dt, J = 15.6, 7.3 Hz, 1H), 6.23 (dt, J = 15.6, 1.2 Hz, 1H), 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); ^{13}C 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 (CH₂), 14.20 (CH₃); Anal. Calc. for C₁₅H₂₇BrO: C, 59.40; H, 8.97; Found: C, 59.40, H, 8.90; MS m/z 261 ($\text{M}^+[\text{Br}]$ -Pr, 1), 259 ($\text{M}^+[\text{Br}]$ -Pr, 1), 209 ($\text{M}^+-\text{CH}_2\text{Br}$, 34), 120 (C₃H₅¹⁸¹Br, 34), 118 (C₃H₅¹⁷⁹Br, 100), 103 (C₂¹⁷⁹Br, 66), 83 (C₅H₇O, 39); HRMS calcd. for C₁₅H₂₇⁷⁹BrONa 325.1138, found 325.1129, calcd. for C₁₅H₂₇⁸¹BrONa 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 premade⁹ catalyst solution (CuI (1 mol%); (*R*)-TolBINAP (1.5 mol%); in anhydrous *t*BuOMe (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.¹⁰) 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 (1:99 Et₂O:pentane) yielded the product as a colorless oil.

(*S*)-S-ethyl 3-(chloromethyl)nonanethioate (**7b**):

[0.5 mmol scale, 83% yield, 94% ee, colorless oil]

$[\alpha]_{\text{D}}^{20}$ = +4.5 (c=1.0, CH₂Cl₂); ^1H NMR δ 3.63 – 3.50 (m, 2H), 2.86 (q, J = 7.5 Hz, 2H), 2.63 (ddd, J = 21.6 Hz, 15.5 Hz, 6.7 Hz, 2H), 2.35 – 2.22 (m, 1H), 1.50 – 1.09 (m, 13H), 0.86 (t, J = 6.7 Hz, 3H); ^{13}C NMR δ 198.51 (C), 48.11 (CH₂), 46.16 (CH₂), 37.56 (CH), 31.78 (CH₂), 31.48 (CH₂), 29.31 (CH₂), 26.60 (CH₂), 23.50 (CH₂), 22.68 (CH₂), 14.81 (CH₃), 14.16 (CH₃); MS m/z 223 ($\text{M}^+[\text{Cl}]$ -Et, 1), 221 ($\text{M}^+[\text{Cl}]$ -Et, 4), 191 ($\text{M}^+[\text{Cl}]$ -Et, 33), 189 ($\text{M}^+[\text{Cl}]$ -Et, 100), 69 (C₄H₅O, 38); HRMS calcd. for C₁₂H₂₄ClOS 251.1231, found 251.1227; *Ee* was determined by chiral GC analysis of methyl 3-(chloromethyl)nonanoate,¹¹ column: Chiraldex-G-TA, 90 °C for 15 min, 90 °C to 170 °C in 40 min, retention times (min): 34.4 ((*R*)-enantiomer), 34.7 ((*S*)-enantiomer).

(*S*)-3-(chloromethyl)-1-phenylhexadecan-5-one (**7e**):

[0.5 mmol scale, 84% yield, 96% ee, colorless oil (which becomes a white solid after storage at -20 °C, with melting point around 20 °C)]

$[\alpha]_{\text{D}}^{20}$ = -5.4 (c=1.0, CH₂Cl₂); ^1H NMR δ 7.34 – 7.25 (m, 2H), 7.23 – 7.16 (m, 3H), 3.66 (dd, J = 3.9 Hz, 1.4 Hz, 2H), 2.75 – 2.54 (m, 3H), 2.49 – 2.36 (m, 4H), 1.85 – 1.52 (m, 4H), 1.37 – 1.22 (m, 16H), 0.96 – 0.87 (m, 3H); ^{13}C NMR δ 209.88 (C), 141.58 (C), 128.45 (CH), 128.29 (CH), 125.98 (CH), 48.35 (CH₂), 44.46 (CH₂), 43.47 (CH₂), 34.90 (CH), 33.41 (CH₂), 33.04 (CH₂), 31.93 (CH₂), 29.63 (2x CH₂), 29.49 (CH₂), 29.42 (CH₂), 29.36 (CH₂), 29.22 (CH₂), 23.85 (CH₂), 22.71 (CH₂), 14.15 (CH₃); MS m/z 328 ($\text{M}^+-\text{H}-\text{Cl}$, 14), 223 (C₁₅H₂₇O, 100), 207 (C₁₄H₂₅O, 45), 129 (29), 91 (C₇H₇, 23); HRMS (APCI in positive mode) calcd. for C₂₃H₃₈ClO 365.2606, found 365.2601; In view of the results for **7b** and **8b**, **7e** was attributed the same *ee* as 1-((1*R*,2*R*)-2-phenethylcyclopropyl)dodecan-1-one (**8e**).

General procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to *trans* 2-substituted cyclopropanecarbothioates:

In a dried Schlenk tube equipped with septum and stirring bar under a N₂ atmosphere, the premade catalyst solution (CuI (1 mol%); (*R*)-TolBINAP (1.5 mol%); in anhydrous *t*BuOMe (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 in 2 h - 2 h 15 min with a syringe pump. The reaction mixture was stirred for 4 h (including addition time) at -78 °C. Subsequently the reaction mixture was allowed to warm up to room temperature and stirred for an additional 2 h. Then the reaction mixture was treated with EtOH (0.4 mL/mmol substrate), followed by a 1 M aq. NH₄Cl-solution (2 mL/mmol substrate). 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 (1:99 Et₂O:pentane) yielded the product as a colorless oil.

The *trans* configuration of the cyclopropanes was established by comparison of the spectra for *cis* and *trans* 2-heptylcyclopropanecarbaldehyde and the spectrum of *trans* 2-heptylcyclopropanecarbaldehyde obtained using our route.

⁹ CuI (1 mol%) and (*R*)-TolBINAP (1.5 mol%) were dissolved in anhydrous *t*BuOMe (8 mL/mmol substrate) and stirred for 1 h to give a clear yellow solution, the solutions were stored under a N₂ atmosphere until use; usually stock solutions for 3-5 mmol substrate were prepared and these solutions have been used after 7 d without change in reactivity

¹⁰ The amount of Grignard reagent is extremely important, just enough is needed to prevent protonolysis of the enolate (by traces of water in the reaction mixture and presumably another mechanism). The acyclic product proved to be inseparable from the cyclopropanes. An excess of Grignard reagent will lead to subsequent double alkylation via 1,2-addition of the products.

¹¹ Transesterification was performed via the following procedure: The substrate (~10 mg) was dissolved in MeOH (0.5 mL) and stirred for 3 h in the presence of K₂CO₃ (excess), then an aq. NH₄Cl-solution (1 M, 0.5 mL) was added and the layers were separated. After extraction with Et₂O (2x 0.5 mL), the combined organic extracts were dried and carefully concentrated to a yellow oil. Filtration over a short SiO₂-column (eluent Et₂O) and evaporation of the solvent yielded the product as a colorless oil.

Furthermore, ^1H NOESY experiments (vide supra) performed with (1*R*,2*R*)-*S*-ethyl 2-methylcyclopropanecarbothioate also confirm the *trans* configuration.

(1*R*,2*R*)-*S*-ethyl 2-hexylcyclopropanecarbothioate (**8b**):

[1.0 mmol scale, 87% yield, 94% ee, colorless oil]

$[\alpha]_{\text{D}}^{20} = -107.2$ ($c=1.0$, CH_2Cl_2); ^1H NMR δ 2.85 (dt, $J = 8.2$ Hz, 6.8 Hz, 2H), 1.71 (dt, $J = 8.1$ Hz, 4.2 Hz, 1H), 1.56 – 1.41 (m, 1H), 1.41 – 1.06 (m, 14H), 0.85 (t, $J = 6.8$ Hz, 3H), 0.75 (ddd, $J = 7.7$ Hz, 6.7 Hz, 4.0 Hz, 1H); ^{13}C NMR δ 198.68 (C), 33.20 (CH_2), 31.86 (CH_2), 30.34 (CH), 29.05 (CH_2), 29.00 (CH_2), 25.56 (CH), 23.30 (CH_2), 22.70 (CH_2), 17.86 (CH_2), 14.95 (CH_3), 14.15 (CH_3); MS m/z 214 (M^+ , 1), 153 ($\text{M}^+ - \text{SEt}$, 100), 69 (C_5H_9 , 49), 55 (C_4H_7 , 83); HRMS calcd. for $\text{C}_{12}\text{H}_{23}\text{OS}$ 251.1464, found 251.1460; *Ee* was determined by chiral GC analysis of methyl 2-hexylcyclopropanecarboxylate,¹¹ column: Chiraldex-G-TA, 80 °C for 50 min, retention times (min): 39.0 ((*R,R*)-enantiomer), 42.0 ((*S,S*)-enantiomer).

(1*R*,2*R*)-*S*-ethyl 2-methylcyclopropanecarbothioate (**8g**):

[1.0 mmol scale, 56% yield (volatile product), 87% ee, colorless oil]

$[\alpha]_{\text{D}}^{20} = -98.3$ ($c=1.0$, CH_2Cl_2); ^1H NMR δ 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), 0.74 (td, $J = 7.2$ Hz, 4.0 Hz, 1H); ^{13}C NMR δ 198.66 (C), 31.37 (CH , d, $J = 168.4$ Hz), 23.33 (CH_2 , t, $J = 141.2$ Hz), 19.75 (CH , d, $J = 169.5$ Hz), 19.14 (CH_2 , t, $J = 165.2$ Hz), 18.02 (CH_3 , q, $J = 126.5$ Hz), 14.98 (CH_3 , q, $J = 128.0$ Hz), trans product according to NOE (see other SI, also for COSY and HQSC); MS m/z 144 (M^+ , 7), 83 ($\text{M}^+ - \text{SEt}$, 100), 55 ($\text{M}^+ - \text{COSEt}$, 29); HRMS calcd. for $\text{C}_7\text{H}_{13}\text{OS}$ 145.0682, found 145.0678; *Ee* was determined by chiral GC analysis of methyl 2-methylcyclopropanecarboxylate,¹¹ column: Chiraldex-G-TA, 50 °C for 30 min, retention times (min): 8.0 ((*S,S*)-enantiomer), 9.8 ((*R,R*)-enantiomer).

(1*R*,2*R*)-*S*-ethyl 2-ethylcyclopropanecarbothioate (**8h**):

[1.0 mmol scale, 67% yield, 95% ee, colorless oil]

$[\alpha]_{\text{D}}^{20} = -109.1$ ($c=1.0$, CH_2Cl_2); ^1H NMR δ 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); ^{13}C NMR (101 MHz, CDCl_3) δ 198.76 (C), 30.10 (CH), 27.16 (CH), 26.32 (CH_2), 23.32 (CH_2), 17.71 (CH_2), 14.95 (CH_3), 13.21 (CH_3); MS m/z 158 (M^+ , 8), 97 ($\text{M}^+ - \text{SEt}$, 100), 55 (C_4H_7 , 92); HRMS calcd. for $\text{C}_8\text{H}_{15}\text{OS}$ 159.0838, found 159.0835; *Ee* was determined by chiral GC analysis of methyl 2-ethylcyclopropanecarboxylate,¹¹ column: Chiraldex-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).

(1*R*,2*R*)-*S*-ethyl 2-isopropylcyclopropanecarbothioate (**8i**):

[1.0 mmol scale, 89% yield, 70% ee, colorless oil]

$[\alpha]_{\text{D}}^{20} = -77.4$ ($c=1.0$, CH_2Cl_2); ^1H NMR δ 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), 0.78 (ddd, $J = 6.2$ Hz, 4.7 Hz, 2.1 Hz, 1H); ^{13}C NMR δ 198.65 (C), 33.20 (CH), 32.36 (CH), 29.48 (CH), 23.28 (CH_2), 21.81 (CH_3), 21.57 (CH_3), 16.84 (CH_2), 14.91 (CH_3); MS m/z 172 (M^+ , 4), 111 ($\text{M}^+ - \text{SEt}$, 57), 69 (C_5H_9 , 49), 55 (C_4H_7 , 100); HRMS calcd. for $\text{C}_9\text{H}_{17}\text{OS}$ 173.0995, found 173.0989; *Ee* was determined by chiral GC analysis of methyl 2-isopropylcyclopropanecarboxylate,¹¹ column: Chiraldex-G-TA, 80 °C for 50 min, retention times (min): 10.4 ((*R,R*)-enantiomer), 11.8 ((*S,S*)-enantiomer).

(1*R*,2*R*)-*S*-ethyl 2-isobutylcyclopropanecarbothioate (**8j**):

[1.0 mmol scale, 91% yield, 84% ee, colorless oil]

$[\alpha]_{\text{D}}^{20} = -114.0$ ($c=1.0$, CH_2Cl_2); ^1H NMR δ 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); ^{13}C NMR δ 198.63 (C), 42.35 (CH_2), 30.43 (CH), 28.52 (CH), 23.96 (CH), 23.30 (CH_2), 22.58 (CH_3), 22.51 (CH_3), 17.87 (CH_2), 14.94 (CH_3); MS m/z 186 (M^+ , 1), 125 ($\text{M}^+ - \text{SEt}$, 92), 97 ($\text{M}^+ - \text{COSEt}$, 29), 55 (C_4H_7 , 100); HRMS calcd. for $\text{C}_{10}\text{H}_{19}\text{OS}$ 187.1151, found 187.1148; *Ee* was determined by chiral GC analysis of methyl 2-isobutylcyclopropanecarboxylate,¹¹ column: Chiraldex-G-TA, 70 °C for 50 min, retention times (min): 12.8 ((*R,R*)-enantiomer), 14.4 ((*S,S*)-enantiomer).

(1*R*,2*R*)-S-ethyl 2-(but-3-enyl)cyclopropanecarbothioate:
[3.0 mmol scale, 88% yield, 94% ee, colorless oil (**8k**)]

$[\alpha]_D^{20} = -111.9$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 5.88 – 5.46 (m, 1H), 5.08 – 4.64 (m, 2H), 2.76 (qd, $J = 7.4$ Hz, 1.9 Hz, 2H), 2.25 – 1.84 (m, 2H), 1.78 – 1.55 (m, 1H), 1.40 (dddd, $J = 13.5$ Hz, 8.1 Hz, 3.8 Hz, 2.0 Hz, 1H), 1.37 – 1.27 (m, 2H), 1.23 (tdd, $J = 6.0$ Hz, 4.5 Hz, 1.7 Hz, 1H), 1.18 – 1.07 (m, 3H), 0.74 – 0.63 (m, 1H); $^{13}\text{C NMR}$ δ 197.84 (C), 137.57 (CH), 114.91 (CH_2), 33.10 (CH_2), 32.40 (CH_2), 29.94 (CH), 24.66 (CH), 23.03 (CH_2), 17.42 (CH_2), 14.77 (CH_3); MS m/z 184 (M^+ , 2), 123 ($\text{M}^+ - \text{SEt}$, 100), 95 ($\text{M}^+ - \text{COSEt}$, 48), 55 (C_4H_7 , 79); HRMS calcd. for $\text{C}_{10}\text{H}_{17}\text{OS}$ 185.0995, found 185.0991; *Ee* was determined by chiral GC analysis of methyl 2-(but-3-enyl)cyclopropanecarboxylate, 11 column: Chiraldex-G-TA, 70 °C for 50 min, retention times (min): 17.4 ((*R,R*)-enantiomer), 19.8 ((*S,S*)-enantiomer).

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

$[\alpha]_D^{20} = -80.0$ ($c=1.0$, value corrected for presence of Grignard dimer (1,8-di-*tert*-butoxyoctane), CH_2Cl_2); $^1\text{H NMR}$ δ 3.35 – 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), 1.16 (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); $^{13}\text{C NMR}$ δ 198.72 (C), 72.54 (CH), 61.48 (CH_2), 33.13 (CH_2), 30.39 (CH_2), 30.31 (CH), 27.67 (CH_3), 25.86 (CH_2), 25.46 (CH), 23.33 (CH_2), 17.92 (CH_2), 14.95 (CH_3), Residual peaks Grignard dimer 72.46 (CH), 61.72 (CH_2), 30.81 (CH_2), 29.61 (CH_2), 27.68 (CH_3), 26.32 (CH_2); MS m/z 258 (M^+ , 1), 141 ($\text{M}^+ - \text{SEt} - \text{tBu}$, 72), 95 (C_7H_{11} , 100), 57 ($\text{C}_3\text{H}_5\text{O}$, 71); HRMS calcd. for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{SNa}$ 281.1546, found 281.1534; *Ee* was determined by chiral GC analysis of methyl 2-(3-*tert*-butoxypropyl)cyclopropanecarboxylate, 11 column Chiraldex-G-TA, 70 °C for 50 min, 70 °C to 120 °C in 100 min; retention times (min): 120.1 (1*R*,2*R*-enantiomer), 121.0 (1*S*,2*S*-enantiomer).

(1*R*,2*R*)-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 (1*R*,2*R*)-S-ethyl 2-(3-*tert*-butoxypropyl)cyclopropanecarbothioate (**8l**) before the derivatization of the thioester to the methyl ester explain this low yield), 96% ee, colorless oil]

$[\alpha]_D^{20} = -56.4$ ($c=0.73$, CH_2Cl_2); $^1\text{H NMR}$ δ 3.65 (s, 3H), 3.32 (t, $J = 6.5$ Hz, 2H), 1.58 – 1.22 (m, 9H), 1.22 – 1.11 (m, 9H), 0.69 (ddd, $J = 7.9$ Hz, 6.1 Hz, 4.1 Hz, 1H); $^{13}\text{C NMR}$ δ 175.13 (C), 72.61 (C), 61.57 (CH_2), 51.73 (CH_3), 33.13 (CH_2), 30.49 (CH_2), 27.72 (CH_3), 25.99 (CH_2), 23.10 (CH), 20.14 (CH), 15.76 (CH_2); MS m/z 213 ($\text{M}^+ - \text{Me}$, 14), 142 ($\text{C}_9\text{H}_{18}\text{O}$, 28), 95 (C_7H_{11} , 100), 57 (C_4H_9 , 62); HRMS calcd. for $\text{C}_{13}\text{H}_{24}\text{O}_3\text{Na}$ 251.1618, found 251.1614; *Ee* was determined by chiral GC analysis, column Chiraldex-G-TA, 70 °C for 50 min, 70 °C to 120 °C in 100 min; retention times (min): 120.1 (1*R*,2*R*-enantiomer), 121.0 (1*S*,2*S*-enantiomer).

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

$[\alpha]_D^{20} = -101.7$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 7.36 – 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); $^{13}\text{C NMR}$ δ 198.39 (C), 141.53 (C), 128.43 (CH), 128.40 (CH), 125.92 (CH), 35.38 (CH_2), 35.04 (CH_2), 30.20 (CH), 24.91 (CH), 23.29 (CH_2), 17.71 (CH_2), 14.96 (CH_3); MS m/z 234 (M^+ , 1), 173 ($\text{M}^+ - \text{SEt}$, 42), 129 ($\text{C}_6\text{H}_5\text{OS}$, 100), 91 (C_7H_7 , 78); HRMS calcd. for $\text{C}_{14}\text{H}_{19}\text{OS}$ 235.1151, found 235.1136; *Ee* was determined by chiral HPLC analysis of methyl 3-(chloromethyl)-5-phenylpentanoate (vide supra), 11 column: chiralcel OB-H, (99:1 heptane: *i*PrOH); retention times (min): 26.0 (*S*-enantiomer (corresponds with the 1*R*,2*R*-enantiomer), 32.7 (*R*-enantiomer (corresponds with the 1*S*,2*S*-enantiomer)).

(*S*)-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]

$[\alpha]_D^{20} = -3.9$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 7.34 – 7.26 (m, 2H), 7.24 – 7.16 (m, 3H), 3.66 (d, $J = 4.5$ Hz, 2H), 2.91 (q, $J = 7.4$ Hz, 2H), 2.80 (dd, $J = 15.5$ Hz, 7.3 Hz, 1H), 2.74 – 2.58 (m, 3H), 2.45 – 2.34 (m, 1H), 1.89 – 1.66 (m, 2H), 1.27 (t, $J = 7.4$ Hz, 3H); $^{13}\text{C NMR}$ δ 198.32 (C), 141.48 (C), 128.58 (CH), 128.41 (CH), 126.15 (CH), 47.91 (CH_2), 45.98 (CH_2), 37.09 (CH), 33.22 (CH_2), 32.95 (CH_2), 23.58 (CH_2), 14.83 (CH_3); MS m/z 211 ($\text{M}^+ [^{37}\text{Cl}] - \text{HSEt}$, 16), 210 ($\text{M}^+ [^{37}\text{Cl}] - \text{HSEt}$, 39), 209 ($\text{M}^+ [^{35}\text{Cl}] - \text{HSEt}$, 48), 208 ($\text{M}^+ [^{35}\text{Cl}] - \text{HSEt}$, 39), 129 ($\text{C}_6\text{H}_5\text{OS}$, 80), 91 (C_7H_7 , 100); HRMS calcd. for $\text{C}_{14}\text{H}_{20}\text{ClOS}$ 271.0918, found 271.0896; *Ee* was

determined by chiral HPLC analysis for methyl 3-(chloromethyl)-5-phenylpentanoate,¹¹ column: chiralcel OB-H, (99:1 heptane:PrOH); retention times (min): 26.0 (*S*-enantiomer), 32.7 (*R*-enantiomer).

(1*R*,2*R*)-*S*-ethyl 2-phenylcyclopropanecarbothioate (**8n**):
[0.5 mmol scale, 50% yield, 26% ee, colorless oil]

$[\alpha]_D^{20} = -125.0$ ($c=2.1$, CH_2Cl_2); $^1\text{H NMR}$ δ 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); $^{13}\text{C NMR}$ δ 197.70 (C), 140.00 (C), 128.63 (CH), 126.74 (CH), 126.32 (CH), 33.86 (CH), 28.48 (CH), 23.60 (CH₂), 18.87 (CH₂), 14.94 (CH₃); MS m/z 206 (M^+ , 18), 151 ($\text{C}_8\text{H}_7\text{OS}$, 65), 145 (M^+-SEt , 79), 127 ($\text{C}_6\text{H}_7\text{OS}$, 79), 117 (M^+-COSEt , 100), 115 ($\text{C}_5\text{H}_7\text{OS}$, 93); HRMS calcd. for $\text{C}_{12}\text{H}_{15}\text{OS}$ 207.0838, found 207.0846; *Ee* was determined by chiral HPLC analysis, column: chiralcel OJ, (99:1 heptane:PrOH); retention times (min): 7.1 (major enantiomer), 9.0 (minor enantiomer)).

(1*R*,2*R*)-methyl 2-phenethylcyclopropanecarboxylate (**8f**):

[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, 0.5 mmol scale, 65% yield (traces of open product), >95% ee; prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates, 1.0 mmol scale, 68% yield, >95% ee, colorless oil]

$[\alpha]_D^{20} = -82.8$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 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); $^{13}\text{C NMR}$ δ 174.78 (C), 141.68 (C), 128.44 (CH), 128.38 (CH), 125.91 (CH), 51.62 (CH₃), 35.50 (CH), 35.04 (CH), 22.62 (CH₂), 20.12 (CH₂), 15.51 (CH₂); MS m/z 173 (M^+-OMe , 1), 130 ($\text{C}_{10}\text{H}_{10}$, 84), 117 (C_9H_9 , 28), 105 (C_7H_7 , 35), 91 (C_7H_7 , 100); HRMS calcd. for $\text{C}_{13}\text{H}_{17}\text{O}_2$ 205.1223, found 205.1209; *Ee* was determined by chiral HPLC analysis, column: chiralcel OB-H, (99:1 heptane:PrOH); retention times (min): 24.7 (1*R*,2*R*-addition product), 25.3 (1*S*,2*S*)-enantiomer).

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

[prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates, 1.0 mmol scale, 87% yield, 98% ee, colorless oil (turning into a white solid after storage at -20°C , with mp around 20°C)]

$[\alpha]_D^{20} = -70.1$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 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); $^{13}\text{C NMR}$ δ 210.62 (C), 43.74 (CH₂), 31.99 (CH₂), 29.69 (2x CH₂), 29.57 (CH₂), 29.54 (CH), 29.51 (CH₂), 29.41 (CH₂), 29.36 (CH₂), 24.18 (CH₂), 22.75 (CH₂), 19.87 (CH), 19.12 (CH₂), 18.17 (CH₃), 14.16 (CH₃); MS m/z 238 (M^+ , 2), 111 ($\text{C}_7\text{H}_{11}\text{O}$, 15), 98 ($\text{C}_6\text{H}_{10}\text{O}$, 100), 83 ($\text{C}_5\text{H}_7\text{O}$, 15), 55 (C_4H_7 , 27); HRMS calcd. for $\text{C}_{16}\text{H}_{31}\text{O}$ 239.2369, found 239.2351; *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): 62.9 ((*R,R*)-enantiomer), 64.4 ((*S,S*)-enantiomer).

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

[prepared via the general procedure for the tandem Cu-catalyzed 1,4-addition-intramolecular trapping reaction using Grignard reagents leading to trans 2-substituted cyclopropanecarbothioates, 1.0 mmol scale, 75% yield, 96% ee, colorless oil (turning into a white solid after storage at -20°C , with mp around 20°C)]

$[\alpha]_D^{20} = -73.8$ ($c=1.0$, CH_2Cl_2); $^1\text{H NMR}$ δ 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); $^{13}\text{C NMR}$ δ 210.46 (C), 141.70 (C), 128.46 (CH), 128.40 (CH), 125.91 (CH), 43.60 (CH₂), 35.65 (CH₂), 35.18 (CH₂), 31.99 (CH₂), 29.71 (CH₂), 29.70 (CH₂), 29.58 (CH₂), 29.52 (CH₂), 29.43 (CH₂), 29.36 (CH₂), 28.50 (CH), 25.19 (CH), 24.10 (CH₂), 22.77 (CH₂), 17.53 (CH₃), 14.20 (CH₃); MS m/z 328 (M^+ , 1), 130 ($\text{C}_{10}\text{H}_{10}$, 100), 91 (C_7H_7 , 25); HRMS calcd. for $\text{C}_{23}\text{H}_{37}\text{O}$ 329.2839, found 329.2816; *Ee* was determined by chiral HPLC analysis, column: chiralcel OJ-H, (99:1 heptane:PrOH); retention times (min): 12.1 (1*R*,2*R*-addition product), 13.3 (1*S*,2*S*)-enantiomer).

Formal syntheses of cascarillic acid: synthesis of (1*R*,2*R*)-2-hexylcyclopropanecarbaldehyde

SI Scheme 1. Formal syntheses of cascarillic acid and grenadamide.^a

^a Conditions: **8**: See Table 2; **9**: DIBAL-H (1.0 M solution in CH₂Cl₂, 1.2 equiv.) in CH₂Cl₂ (0.4 M), -78 °C, 3 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 N₂ atmosphere the thioester (1.0 equiv.) was dissolved in anhydrous CH₂Cl₂ (2.5 mL/mmol substrate). After 5 min stirring at room temperature the mixture was cooled to -78 °C and DIBAL-H (1.2 equiv.) was added drop-wise. The reaction mixture was stirred for 3 h at -78 °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 rt and the layers were separated. After extraction with CH₂Cl₂ (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 Et₂O:pentane) yielded the pure product.

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

$[\alpha]_D^{20} = -36.9$ (c=1.0, CH₂Cl₂). Literature value:¹² $[\alpha]_D^{20} = -26.0$ (c=0.35, CH₂Cl₂) for the (1*R*,2*R*)-enantiomer. Experimental data in accordance with data reported in ref 12.

Formal synthesis of grenadamide (**8p**): synthesis of (1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde

(1*R*,2*R*)-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]

$[\alpha]_D^{20} = -107.9$ (c=1.0, CH₂Cl₂); ¹H NMR δ 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 δ 198.59 (C), 33.20 (CH₂), 31.90 (CH₂), 30.32 (CH), 29.31 (CH₂), 29.29 (CH₂), 29.08 (CH₂), 25.51 (CH), 23.28 (CH₂), 22.72 (CH₂), 17.81 (CH₂), 14.93 (CH₃), 14.15 (CH₃); MS *m/z* 228 (M⁺, 1), 167 (M⁺-SEt, 92), 69 (C₅H₉, 38), 55 (C₄H₇, 93); HRMS calcd. for C₁₃H₂₅OS 229.1621, found 229.1618; *Ee* was determined by chiral GC analysis for methyl 2-heptylcyclopropanoate,¹¹ column: Chiraldex-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).

(1*R*,2*R*)-2-heptylcyclopropanecarbaldehyde (**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]

$[\alpha]_D^{20} = -43.9$ (c=1.0, CHCl₃). Literature value:¹³ $[\alpha]_D^{20} = +41.4$ (c=1.45, CHCl₃) for the trans (1*S*,2*S*)-enantiomer. Experimental data in accordance with data reported in ref 13.

¹² M. Cheeseman, S. D. Bull, *Synlett* **2006**, 1119-1121.

¹³ J. R. Al Dulayymi, M. S. Baird, K. Jones, *Tetrahedron* **2004**, 60, 341-345.

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

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

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

(S)-S-ethyl 3-(chloromethyl)nonanethioate (**7b**):

racemic methyl 3-(chloromethyl)nonanoate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.159	1	34.447	MF		96.467	50.140	0.000	0.000
0.162	2	34.842	FM		95.928	49.860	0.000	0.000

(S)-methyl 3-(chloromethyl)nonanoate:

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.137	1	34.385	MM		35.418	2.987	0.000	0.000
0.164	2	34.747	MM		1150.189	97.013	0.000	0.000

(*S*)-3-(chloromethyl)-1-phenylhexadecan-5-one (**7e**):

(1*R*,2*R*)-*S*-ethyl 2-hexylcyclopropanecarbothioate (**8b**):

racemic methyl 2-hexylcyclopropanecarboxylate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.628	1	38.937	MM		382.754	50.348	0.000	0.000
0.675	2	41.816	MM		377.469	49.652	0.000	0.000

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

signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.567	1	38.989	MM		684.529	96.983	0.000	0.000
0.608	2	41.977	MM		21.293	3.017	0.000	0.000

(1*R*,2*R*)-*S*-ethyl 2-methylcyclopropanecarbothioate (**8g**): spectra contain traces of (*S*)-*S*-ethyl 4-chloro-3-methylbutanethioate and Et₂O

Coupled ^{13}C

HQSC

COSY

NOESY

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:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.211	1	8.009	MM		41.077	50.940	0.000	0.000
0.269	2	9.775	MM		39.560	49.060	0.000	0.000

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

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.184	1	8.018	MM		155.734	93.467	0.000	0.000
0.217	2	9.832	MM		10.885	6.533	0.000	0.000

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

racemic methyl 2-ethylcyclopropanecarboxylate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.105	1	40.979	MM		7.599	48.753	0.000	0.000
0.097	2	41.556	MM		7.988	51.247	0.000	0.000

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

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.092	1	41.002	MM		1.028	2.409	0.000	0.000
0.085	2	41.557	MM		41.643	97.591	0.000	0.000

(1*R*,2*R*)-*S*-ethyl 2-isopropylcyclopropanecarbothioate (**8i**): spectra contain traces of (*R*)-*S*-ethyl 3-(chloromethyl)-4-methylpentanethioate

racemic methyl 2-isopropylcyclopropanecarboxylate:

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.230	1	10.457	MM		168.948	50.146	0.000	0.000
0.271	2	11.862	MM		167.964	49.854	0.000	0.000

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

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.218	1	10.416	MM		129.495	84.934	0.000	0.000
0.237	2	11.840	MM		22.970	15.066	0.000	0.000

(1*R*,2*R*)-*S*-ethyl 2-isobutylcyclopropanecarbothioate (**8j**):

racemic methyl 2-isobutylcyclopropanecarboxylate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.253	1	12.897	MM		119.252	49.992	0.000	0.000
0.291	2	14.528	MM		119.290	50.008	0.000	0.000

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

Peak #	RT [min]	Type	Name	Width [min]	Area	Area %	Response	Amount
1	12.794	MM		0.236	383.258	92.149	0.000	0.000
2	14.437	MM		0.258	32.654	7.851	0.000	0.000

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

racemic methyl 2-(but-3-enyl)cyclopropanecarboxylate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.324	1	17.339	MM		234.579	50.641	0.000	0.000
0.373	2	19.559	MM		228.640	49.359	0.000	0.000

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

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.290	1	17.406	MM		362.197	97.058	0.000	0.000
0.345	2	19.754	MM		10.979	2.942	0.000	0.000

(1*R*,2*R*)-*S*-ethyl 2-(3-*tert*-butoxypropyl)cyclopropanecarbothioate (**81**): 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:

(1*R*,2*R*)-methyl 2-(3-*tert*-butoxypropyl)cyclopropanecarboxylate:

(1*R*,2*R*)-methyl 2-(3-*tert*-butoxypropyl)cyclopropanecarboxylate: spectra contain traces of EtOAc and H₂O.

(1*R*,2*R*)-methyl 2-phenethylcyclopropanecarbothioate (**8m**): spectra contain traces of (*S*)-*S*-ethyl 3-(chloromethyl)-5-phenylpentanethioate

racemic *trans* 2-phenethylcyclopropanecarboxylate:

1: 210
nm, 4 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,364 Minutes	24,364	13081391	28,887
2	Peak @ 25,072 Minutes	25,072	14691453	32,442
3	Peak @ 26,084 Minutes	26,084	8809979	19,454
4	Peak @ 32,436 Minutes	32,436	8702477	19,217
Totals			45285300	100,000

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

1: 210
nm, 4 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,860 Minutes	24,860	6015520	89,270
2	Peak @ 25,400 Minutes	25,400	723028	10,730
Totals			6738548	100,000

(S)-S-ethyl 3-(chloromethyl)-5-phenylpentanethioate: spectra contain traces of (1R,2R)-S-ethyl 2-phenethylcyclopropanecarbothioate

(1*R*,2*R*)-*S*-ethyl 2-phenylcyclopropanecarbothioate (**8n**): spectra contain traces of CH₂Cl₂ and H₂O

Racemic *trans* S-ethyl 2-phenylcyclopropanecarbothioate:

1: 230 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1		6.485	30793651	48.88
2		8.352	32201266	51.12
Totals			62994917	100.00

Enantioenriched *trans* S-ethyl 2-phenylcyclopropanecarbothioate:

1: 230 nm, 8 nm

Pk #	Name	Retention Time	Area	Area Percent
1		7.072	12441702	63.07
2		8.971	7285753	36.93
Totals			19727455	100.00

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

racemic *trans* 1-((1*R*,2*R*)-2-phenethylcyclopropyl)dodecan-1-one:

1: 215
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 12,128 Minutes	12,128	1419000	49,234
2	Peak @ 13,560 Minutes	13,560	1463172	50,766
Totals			2882172	100,000

1-((1*R*,2*R*)-2-phenethylcyclopropyl)dodecan-1-one:

1: 210
nm, 2 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 12,088 Minutes	12,088	9818521	97,958
2	Peak @ 13,320 Minutes	13,320	204670	2,042
Totals			10023191	100,000

1-((1*R*,2*R*)-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:

Signal 1: FID1 A,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.289	1	63.388	MM		7.346	50.869	0.000	0.000
0.265	2	64.407	MM		7.095	49.131	0.000	0.000

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

Signal 1: FID1 A,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.465	1	62.885	MM		1307.954	99.142	0.000	0.000
0.339	2	64.373	MM		11.317	0.858	0.000	0.000

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

racemic *trans* methyl 2-phenethylcyclopropanecarboxylate:

1: 210
nm, 4 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,364 Minutes	24,364	13081391	28,887
2	Peak @ 25,072 Minutes	25,072	14691453	32,442
3	Peak @ 26,084 Minutes	26,084	8809979	19,454
4	Peak @ 32,436 Minutes	32,436	8702477	19,217
Totals			45285300	100,000

(1*R*,2*R*)-methyl 2-phenethylcyclopropanecarboxylate:

1: 210
nm, 4 nm
Results

Pk #	Name	Retention Time	Area	Area Percent
1	Peak @ 24,732 Minutes	24,732	7410399	98,032
2	Peak @ 25,320 Minutes	25,320	148786	1,968
Totals			7559185	100,000

(1*R*,2*R*)-*S*-ethyl 2-heptylcyclopropanecarbothioate (**8p**):

racemic methyl 2-heptylcyclopropanoate:

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.172	1	53.005	MM		524.592	48.678	0.000	0.000
0.145	2	53.580	MM		553.079	51.322	0.000	0.000

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

Signal 2: FID2 B,

Width [min]	Peak #	RT [min]	Type	Name	Area	Area %	Response	Amount
0.130	1	53.061	BB		297.200	97.456	0.000	0.000
0.108	2	53.608	MM		7.757	2.544	0.000	0.000