Carbohydrate-Derived Bis(oxazoline) Ligand in the Total Synthesis of Grenadamide

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Abstract: Using an optimised carbohydrate-based bis(oxazoline) ligand and copper(I) triflate, unactivated aliphatic alkenes were cyclopropanated with simple ethyl diazoacetate, giving the corresponding products in good yields and high stereoselectivities. The *trans*-disubstituted cyclopropyl carboxylic acid ester derived from 1-nonene was subsequently used as the key intermediate for the synthesis of the (+)-enantiomer of the natural product (–)-grenadamide. The efficient and high-yielding approach towards grenadamide reported here is the first to utilise asymmetric cyclopropanation for the construction of the chiral cyclopropyl unit.

Key words: carbohydrates, ligand design, asymmetric catalysis, natural products, cyclopropanation

The cyclopropane moiety represents an important scaffold in numerous natural products.[1] Compounds with this subunit can be found in marine cyanobacteria, which are well-known as an abundant source of biologically active and structurally unique secondary metabolites.[2]

In 1998, Gerwick reported the isolation of the three natural products: grenadadiene (**1**), debromgrenadadiene (**2**) and grenadamide (**3**), from the lipid extract of the marine cyanobacteria *Lyngbya majuscula* found in Grenada in the southern Carribean.[3] All three contain a *trans*-substituted cyclopropanated fatty acid derivative as a core structural feature (Figure 1). In biological testing, these compounds show modest binding activity to the cannabinoid receptor, brine shrimp toxicity as well as activity against some cancer cell lines.[3]

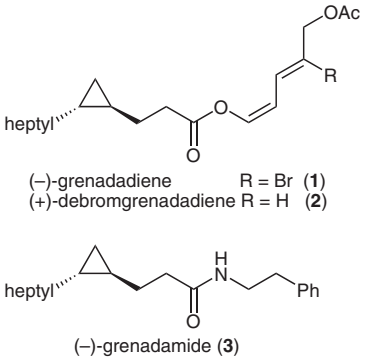

Figure 1 Cyclopropanated natural products isolated from cyanobacterium *Lyngbya majuscula*

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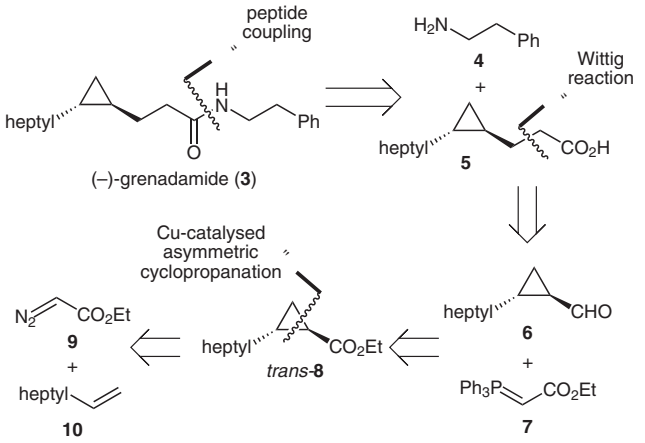
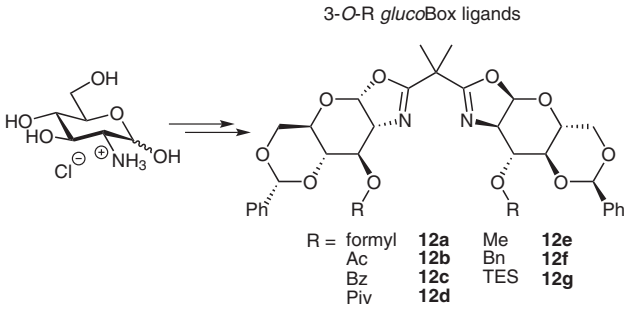
The absolute configuration of grenadamide (**3**) was proved by Baird et al. by the total synthesis of the non-natural (+)-enantiomer of **3** via an enzymatic desymmetrisation of a *meso*-cyclopropyl diol and a base-mediated epimerisation to access the chiral cyclopropane unit.[4] Further total syntheses were reported by the groups of Bull, Taylor and Piva.[5–7] Bull et al. prepared natural (–)-grenadamide employing a chiral auxiliary approach to create temporary stereocentres, which were used to direct a substrate-controlled stereoselective Simmons–Smith cyclopropanation. These temporary stereocentres had to be subsequently removed.[5] Taylor et al. reported the total synthesis of both (+)- and (–)-grenadamide by a racemic route and subsequent enantiomeric resolution by coupling of the cyclopropyl carboxylic acid precursor to the Evans auxiliary.[6] Piva et al. published a synthesis of racemic (±)-grenadamide without resolution.[7]

Of the many approaches to the synthesis of chiral cyclopropane derivatives,[8] asymmetric cyclopropanation of alkenes with diazo esters using chiral transition-metal catalysts is especially attractive. Therefore, it seems surprising that, to date, no total synthesis of grenadamide has employed this strategy to construct the chiral cyclopropane unit. Scheme 1 outlines a retrosynthetic analysis of (–)-grenadamide (**3**) via cyclopropyl carbaldehyde **6**, which is accessible by a route previously employed in Baird's total synthesis.[4] Aldehyde **6** can easily be obtained from chiral cyclopropane carboxylic ester *trans*-**8**, which, in turn, may be prepared by copper(I)-catalysed asymmetric cyclopropanation in a single step from ethyl diazoacetate (**9**) and non-1-ene (**10**).



Scheme 1 Retrosynthetic analysis of (–)-grenadamide (**3**) and preparation of chiral cyclopropyl carboxylic acid *trans*-**8** by asymmetric cyclopropanation

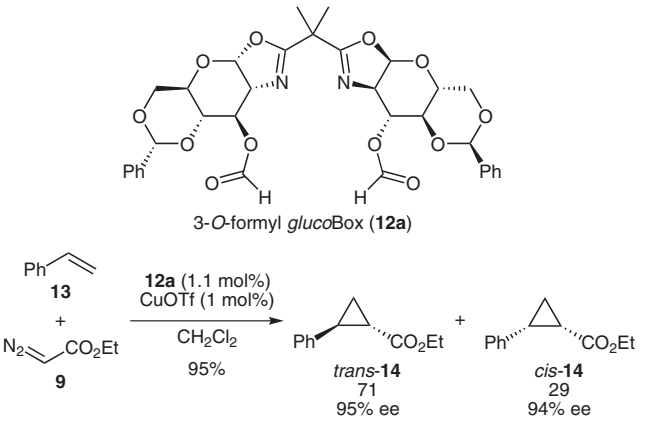
The focus of research in our group is on the design of new ligand systems based on carbohydrates and their application in stereoselective metal catalysis. The first examples of carbohydrate-based ligands were published independently by Cullen,[9] Thompson,[10] Selke[11] and Descotes[12] thirty years ago. After this seminal work, which clearly demonstrated their high efficiency, carbohydrate-based ligands have occurred only rarely compared to structures derived from other chiral pool compounds. The high potential of carbohydrates as starting material for ligand design has only recently started to be recognised.[13]



Scheme 2 Bis(oxazoline) ligands **12a–g** derived from D-glucosamine hydrochloride (**11**)

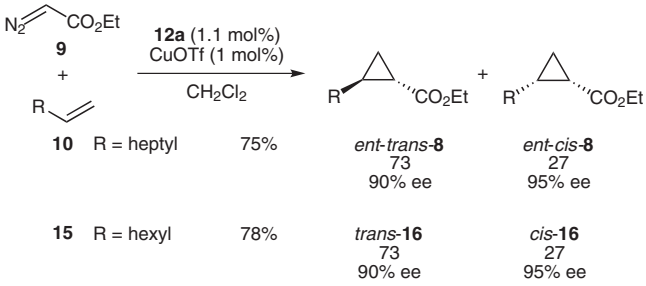
Bis(oxazolines)[14] (box) and pyridylbis(oxazolines)[15] (pybox) constitute one of the most successful classes of chiral ligands in asymmetric synthesis.[14,15] We have recently introduced new box and pybox ligands derived from inexpensive D-glucosamine hydrochloride (**11**),[16a,b] and developed a flexible route towards structural variants of the basic pyranoside ligand structure.[16c–e] (Scheme 2). By this approach we were able to optimise the carbohydrate-derived box ligands for the asymmetric cyclopropanation of styrene (**13**) with ethyl diazoacetate (**9**), which is a benchmark reaction for new box ligands using copper(I) salts.[17] Our optimisation studies, which were performed by systematic variation of the 3-O-substituents, revealed a strong dependence of the enantioselectivity of the cyclopropanation reaction on both the steric demand and the electronic nature of the residues at this position.[16e] The best result was obtained with the 3-*O*-formyl *gluco*Box ligand (**12a**), which gave the diastereomeric cyclopropanes *trans*-**14** and *cis*-**14** (*trans*/*cis* = 71:29) both in excellent stereoselectivity (Scheme 3).

Whereas numerous ligands promote the copper-catalysed cyclopropanation of aromatic or other activated alkene derivatives in excellent stereoselectivity and high yields,[8] non-activated, aliphatic alkenes are still challenging substrates. In many instances, the corresponding products are obtained in high selectivity (90% ee and above) but only in poor yields (below 40% combined yield for the *trans*/*cis* product mixture).[18] Catalyst systems leading to both good yields and stereoselectivities are comparatively rare[19] and, generally, diazoesters with sterically demanding alcohol residues, such as the 2,6-di-*tert*-butyl-4-methylphenyl (BHT) group or containing menthyl residues introducing an additional chiral element, are necessary to



Scheme 3 3-*O*-Formyl *gluco*Box (**12a**) in the copper(I)-mediated cyclopropanation of styrene (**13**)

achieve high levels of stereoinduction.[18,19] Therefore, we were very pleased to find that the copper(I) complex of our optimised ligand 3-*O*-formyl *gluco*Box (**12a**) led to both high yield and stereoselectivity when either 1-nonene (**10**) or 1-octene (**15**) and a simple ethyl diazoacetate were used as substrates, even when the reaction was performed on a multi-gram scale. The cyclopropyl carboxylic esters *ent-trans*-**8** and *ent-cis*-**8** (*trans*/*cis* = 73:27) were obtained from 1-nonene (**10**) in 75% combined yield and in 90% ee or in 94% ee, respectively; the same reaction with 1-octene led to almost the same results (Scheme 4).

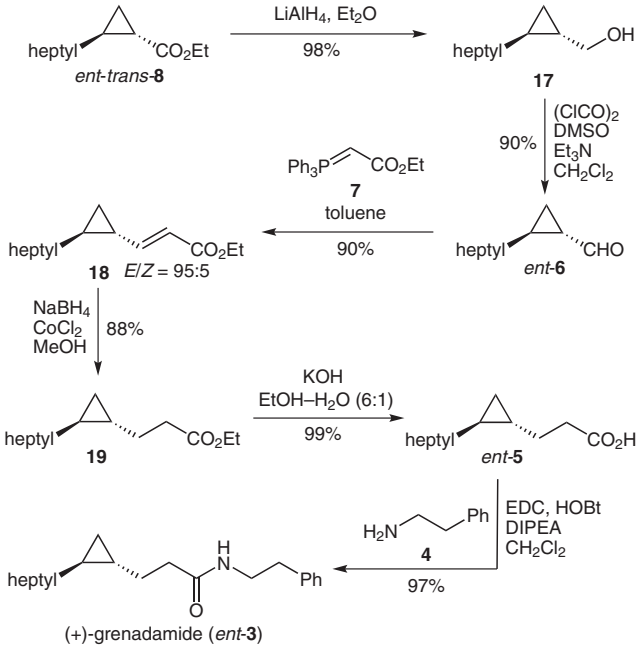


Scheme 4 Asymmetric cyclopropanation of 1-nonene (**10**) and 1-octene (**15**) using optimised ligand 3-*O*-formyl *gluco*Box (**12a**)

The two diastereomeric products *ent-trans*-**8** and *ent-cis*-**8** were separated by column chromatography and, after obtaining approximately one gram of pure enantioenriched ester *ent-trans*-**8** from the cyclopropanation reaction, we had the starting material for the total synthesis of grenadamide in hand. Due to the configuration of our carbohydrate-derived catalyst ligand **12a**, the cyclopropyl unit in *ent-trans*-**8** has the opposite configuration to that of natural (–)-grenadamide (**3**), leading to the synthesis of the non-natural (+)-enantiomer of **3**.

According to the retrosynthesis outlined in Scheme 1, cyclopropyl carboxylic ester *ent-trans*-**8** was transformed into the corresponding aldehyde *ent*-**6** by reduction with lithium aluminium hydride to alcohol **17**, followed by Swern oxidation.[20] Subsequently, aldehyde *ent*-**6** was used in a Wittig olefination with stabilised ylide **7** to give

α,β-unsaturated ester **18** in an *E*/*Z* ratio of 95:5.[4] Due to the fact that β-cyclopropyl acrylates are prone to opening of the strained three-membered ring under standard hydrogenation conditions, special methods were necessary for the next step. To avoid ring opening, α,β-unsaturated ester **18** was treated with sodium borohydride in the presence of a catalytic amount of cobalt(II) chloride hexahydrate.[21] Under these conditions, saturated cyclopropyl ester **19** was obtained without formation of any ring-opened by-products. Saponification of **19**[4] to acid *ent*-**5**, followed by coupling with β-phenethylamine (**4**) under standard conditions[22] gave (+)-grenadamide (*ent*-**3**). The complete synthetic pathway is summarised in Scheme 5.



Scheme 5 Synthesis of (+)-grenadamide (*ent*-**3**) from cyclopropane carboxylic ester *ent*-*trans*-**8** as key intermediate

In conclusion, we have successfully demonstrated the application of our carbohydrate-based bis(oxazoline) ligand 3-*O*-formyl *gluco*Box (**12a**) as a tool in natural product synthesis. With **12a** as chiral ligand in an enantioselective, copper(I)-catalysed cyclopropanation as the key step, 1-nonene (**10**) and ethyl diazoacetate (**9**) gave cyclopropyl carboxylic ester *ent*-*trans*-**8** in good yield and 90% ee, even on a multigram scale. Starting from *ent*-*trans*-**8** as key intermediate, we completed the total synthesis of (+)-grenadamide (*ent*-**3**) in six further steps. We will now apply our ligand to other aliphatic alkene substrates to access cyclopropanated intermediates for other natural products containing this structural motif. Efforts towards the synthesis of *pseudo* enantiomeric carbohydrate bis(oxazoline) ligands using various D-hexose scaffolds are currently under way. A suitable *pseudo* enantiomeric ligand would allow access to the natural enantiomer of grenadamide by the route described in this publication.

Anhydrous solvents were obtained by distillation from appropriate drying reagents under a nitrogen atmosphere (CH_2Cl_2 was distilled from CaH_2, MeOH was distilled from Mg turnings) or were purchased in anhydrous form from commercial sources (DMF, Et_2O and toluene from ACROS) and used as received. All reactions involving reagents that were sensitive to air and moisture were carried out under a nitrogen atmosphere (glove box and/or Schlenk techniques). Reactions were monitored by TLC on 60 F254 aluminium plates (Merck) with detection by UV light and/or charring with $KMnO_4$ solution. Flash chromatography was performed on Merck silica (grain size 40–63 μm). NMR spectra were recorded with an AVS 400 instrument (Bruker) at 400 MHz (^{1}H) or at 100 MHz (^{13}C). $CDCl_3$ was used as solvent and spectra were calibrated against the residual solvent peak (^{1}H NMR, $CHCl_3$: δ = 7.24 ppm; ^{13}C NMR, $CHCl_3$: δ = 77.0 ppm). Electrospray (ESI) mass spectra were recorded with a Micromass LCT device (Waters); injection into the HPLC instrument (Waters) was performed in loop modus. Optical rotations were recorded with a Perkin–Elmer 451 instrument under the following standard conditions: r.t., wavelength 589.3 nm (sodium D-line), cell length 1 dm, solvent and sample concentration (in 10 mg mL^{-1}) are given with the individual experiment. Melting points were recorded with an OptiMelt device from SRS. Chiral GC experiments were carried out with an HP 5890-II device (Hewlett–Packard) with a flame-ionisation detector and hydrogen as carrier gas in constant flow modus. Starting temperature was 40 °C (temp. gradient: 0.60 °C min^{-1}). A Hydrodex-β PM capillary column (50 m, 0.25 mm, 723370, Macherey–Nagel) was used for separation of the enantiomers. Determination of enantiomeric excesses by gas chromatography: a racemic sample of the product was analysed by GC on the chiral stationary phase to obtain the retention times of both enantiomers. Then an enantiomerically enriched sample was injected and the enantiomeric excess was determined from the resulting chromatogram by peak integration.

Ethyl (1*S*,2*S*)-2-Heptylcyclopropanecarboxylate (*ent*-*trans*-8) and Ethyl (1*S*,2*R*)-2-Heptylcyclopropanecarboxylate (*ent*-*cis*-8)

In a glove box, CuOTf·0.5C_6H_6 (81 mg, 160 μmol, 1 mol%) and 3-*O*-formyl *gluco*Box (**12a**; 117 mg, 180 μmol, 1.1 mol%) were placed into a flame-dried flask, dissolved in anhydrous CH_2Cl_2 (25 mL) and the resulting mixture was stirred at r.t. for 1 h. To this preformed catalyst solution was added 1-nonene (**10**; 10.00 g, 79.21 mmol). The reaction mixture was cooled to –5 °C and ethyl diazoacetate (**9**; 1.81 g, 15.84 mmol) dissolved in anhydrous CH_2Cl_2 (20 mL) was added slowly via a syringe pump (flow rate: 0.35 mL/h). After stirring for an additional 16 h at –5 °C, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (PE–Et_2O, 100:1) to yield esters *ent*-*trans*-**8** and *ent*-*cis*-**8** (2.52 g, 11.88 mmol, 75%) as a colourless oil (*trans*/*cis* = 73:27). The mixture of diastereomeric esters was separated via flash chromatography on silica gel (PE–Et_2O, 100:1) to give the pure compound *ent*-*trans*-**8** (1.62 g, 7.62 mmol, 48% total yield based on starting material **9**).

$[\alpha]_D^{20}$ +57.9 (*c* 0.96, $CHCl_3$) (*ent*-*trans*-**8**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.63–0.67 (m, 1 H, CH_2), 0.85 (t, *J* = 6.9 Hz, 3 H, OCH_2CH_3), 1.09–1.13 [m, 1 H, $CH_3(CH_2)_5CH$], 1.21–1.38 (m, 17 H), 4.08 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.2, 15.4, 20.2, 22.6, 22.9, 29.0, 29.23, 29.24, 31.8, 33.0, 60.2, 174.6.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{24}O_2Na$: 235.1668; found: 235.1676.

Retention times (chiral GC):
Racemic mixture *ent*-*cis*-**8**: t_R = 112.93 min, t_R = 114.17 min.
Product *ent*-*cis*-**8**: t_R = 112.97 min (major), t_R = 114.36 min (minor).
Racemic mixture *ent*-*trans*-**8**: t_R = 117.45 min, t_R = 118.27 min.

Product *ent*-*trans*-**8**: t_R = 117.71 min (minor), t_R = 118.20 min (major).

Ethyl (1*S*,2*S*)-2-Hexylcyclopropanecarboxylate (*trans*-16) and Ethyl (1*S*,2*R*)-2-Hexylcyclopropanecarboxylate (*cis*-16)

In a glove box, CuOTf·0.5C_6H_6 (10 mg, 20 μmol, 1 mol%) and 3-*O*-formyl *gluco*Box (**12a**; 14 mg, 18 μmol, 1.1 mol%) were placed into a flame-dried flask, dissolved in anhydrous CH_2Cl_2 (5 mL) and the resulting mixture was stirred at r.t. for 1 h. To this preformed catalyst solution was added 1-octene (**15**; 1.12 g, 1.43 mL, 10.00 mmol). The reaction mixture was cooled to –5 °C and ethyl diazoacetate (**9**; 228 mg, 209 μL, 2.00 mmol) dissolved in anhydrous CH_2Cl_2 (3 mL) was added slowly via a syringe pump (flow rate: 0.35 mL/h). After stirring for an additional 16 h at –5 °C, the solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (PE–Et_2O, 100:1) to yield *trans*-**16** and *cis*-**16** (309 mg, 1.56 mmol, 78%) as a colourless oil (*trans*/*cis* = 73:27). Ester *trans*-**16** was separated by flash chromatography on silica gel (PE–Et_2O, 100:1).

$[\alpha]_D^{20}$ +61.9 (*c* 1.17, $CHCl_3$) (*trans*-**16**).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.62–0.68 (m, 1 H), 0.85 (t, *J* = 7.0 Hz, 3 H), 1.08–1.14 (m, 1 H), 1.19–1.41 (m, 15 H), 4.09 (q, *J* = 7.2 Hz, 2 H, OCH_2CH_3).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.2, 15.4, 20.2, 22.6, 22.9, 28.9, 29.0, 31.7, 33.0, 60.2, 174.6.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{12}H_{22}O_2Na$: 221.1512; found: 221.1519.

Retention times (chiral GC):
Racemic mixture *cis*-**16**: t_R = 93.68 min, t_R = 94.65 min.
Product *cis*-**16**: t_R = 93.64 min (major), t_R = 94.70 min (minor).
Racemic mixture *trans*-**16**: t_R = 98.70 min, t_R = 99.69 min.
Product *trans*-**16**: t_R = 98.84 min (minor), t_R = 99.58 min (major).

(1*S*,2*S*)-2-(Heptylcyclopropyl)methanol (17)

LAH (331 mg, 8.70 mmol) was added at 0 °C to a solution of *ent*-*trans*-**8** (925 mg, 4.35 mmol) in anhydrous Et_2O (30 mL) and the resulting suspension was stirred at r.t. for 1 h. The reaction mixture was treated with sat. aq Na_2SO_4 (200 mL) and extracted with Et_2O (2 × 200 mL). The combined organic layers were washed with brine (2 × 100 mL), dried over Na_2SO_4 and the solvent was removed under reduced pressure. The residue was purified by flash chromatography on silica gel (PE–EtOAc, 6:1) to yield alcohol **17**.

Yield: 730 mg (4.29 mmol, 98%); colourless oil; $[\alpha]_D^{20}$ +21.2 (*c* 1.11, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.26–0.30 (m, 1 H), 0.31–0.34 (m, 1 H), 0.55–0.58 (m, 1 H), 0.67–0.83 (m, 1 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 1.14–1.37 (m, 12 H), 1.54 (s, 1 H, OH), 3.33–3.49 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.9, 14.0, 17.2, 21.1, 22.6, 29.31, 29.39, 29.6, 31.8, 33.5, 67.2.

MS (EI, 70 eV): *m*/*z* (%) = 152.1 (100) [M – H_2O]$^+$.

(1*S*,2*S*)-2-Heptylcyclopropanecarbaldehyde (*ent*-6)

Oxalyl chloride (1.57 g, 1.06 mL, 12.33 mmol) was disolved in anhydrous CH_2Cl_2 (50 mL) and the mixture was cooled to –78 °C. DMSO (1.93 g, 1.75 mL, 24.66 mmol) was added dropwise and the reaction mixture was stirred for 15 min at –78 °C. Alcohol **17** (700 mg, 4.11 mmol) was dissolved in anhydrous CH_2Cl_2 (10 mL) and added dropwise to the reaction mixture. After stirring for another 30 min at –78 °C, Et_3N (3.74 g, 5.12 mL, 36.99 mmol) was added dropwise and the solution was warmed to r.t. The reaction mixture was diluted with CH_2Cl_2 (150 mL) and washed with sat. aq NH_4Cl (150 mL). The organic layer was separated, dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel (PE–EtOAc, 20:1) yielded aldehyde *ent*-**6**.

Yield: 621 mg (3.69 mmol, 90%); colourless oil; $[\alpha]_D^{20}$ +39.9 (*c* 1.01, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.0 Hz, 3 H), 0.87–0.91 (m, 1 H), 1.17–1.38 (m, 13 H), 1.39–1.46 (m, 1 H), 1.55–1.61 (m, 1 H), 8.96 (d, *J* = 5.6 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.8, 22.6, 22.7, 29.0, 29.17, 29.18, 30.5, 31.7, 32.6, 201.0.

MS (EI, 70 eV): *m*/*z* (%) = 168.1 (100) [M]$^+$.

Ethyl (*E*)-3-[(1*S*,2*S*)-2-Heptylcyclopropyl]acrylate (18)

Aldehyde *ent*-**6** (584 mg, 3.47 mmol) was dissolved in anhydrous toluene (10 mL) and added to a solution of (ethoxycarbonylmethylene)triphenylphosphorane (**7**; 1.82 g, 5.21 mmol) in toluene (20 mL). After stirring for 36 h at r.t., the reaction mixture was concentrated under reduced pressure and the residue was heated at reflux in PE–Et_2O (5:2; 50 mL) for 10 min. The precipitate was filtered off and washed with PE–Et_2O (1:1; 2 × 50 mL). The solvent was removed under reduced pressure and the residue was purified by flash chromatography on silica gel (PE–EtOAc, 50:1) to give the *E*-configured acrylic ester **18**.

Yield: 745 mg (3.13 mmol, 90%); colourless oil; $[\alpha]_D^{20}$ +63.6 (*c* 1.16, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.70–0.74 (m, 1 H), 0.75–0.81 (m, 1 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 0.92–1.02 (m, 1 H), 1.19–1.37 (m, 16 H), 4.14 (q, *J* = 7.1 Hz, 2 H), 5.80 (d, *J* = 15.5 Hz, 1 H), 6.45 (dd, *J* = 10.1, 15.5 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0, 14.3, 16.0, 22.1, 22.6, 23.3, 29.1, 29.25, 29.29, 31.8, 33.5, 59.9, 117.3, 153.8, 166.8.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{26}O_2Na$: 261.1825; found: 261.1821.

Ethyl 3-[(1*S*,2*S*)-2-Heptylcyclopropyl]propionate (19)

$CoCl_2·6H_2O$ (131 mg, 0.55 mmol) was added to a solution of acrylic ester **18** (685 mg, 2.87 mmol) in anhydrous MeOH (25 mL) and the reaction mixture was stirred at r.t. for 30 min. Then, $NaBH_4$ (434 mg, 11.48 mml) suspended in anhydrous DMF (10 mL) was added and the reaction mixture was subsequently stirred for 30 min. The reaction was quenched with H_2O (25 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with H_2O (3 × 320 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel (PE–EtOAc, 50:1) yielded reduced ester **19**.

Yield: 610 mg (2.53 mmol, 88%); colourless oil; $[\alpha]_D^{20}$ +11.1 (*c* 1.02, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.13–0.21 (m, 2 H), 0.34–0.46 (m, 2 H), 0.85 (t, *J* = 6.9 Hz, 3 H), 1.03–1.12 (m, 1 H), 1.16–1.32 (m, 14 H), 1.41–1.58 (m, 2 H), 2.34 (t, *J* = 7.5 Hz, 2 H), 4.10 (q, *J* = 7.2 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 14.0, 14.2, 18.1, 18.8, 22.6, 29.3, 29.4, 29.6, 29.7, 31.8, 34.1, 34.5, 60.1, 173.7.

HRMS (ESI+): *m*/*z* [M + Na]$^+$ calcd for $C_{15}H_{28}NaO_2$: 263.1982; found: 263.1979.

3-[(1*S*,2*S*)-2-Heptylcyclopropyl]propionic Acid (*ent*-5)

Ester **19** (562 mg, 2.34 mmol) was added to a solution of KOH (1.31 g, 23.40 mmol) in EtOH (18 mL) and H_2O (3 mL). The mixture was stirred for 2 h at r.t., diluted with H_2O (30 mL) and Et_2O (50 mL) and acidified to pH 2 with H_2SO_4 (5%). The organic layer was separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to yield acid *ent*-**5**.

Yield: 495 mg (2.33 mmol, 99%); colourless oil; $[\alpha]_D^{20}$ +13.5 (*c* 1.03, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.15–0.24 (m, 2 H), 0.37–0.49 (m, 2 H), 0.86 (t, *J* = 6.9 Hz, 3 H), 1.08–1.14 (m, 1 H), 1.16–1.35 (m, 12 H), 1.49–1.54 (m, 2 H), 2.41 (t, *J* = 7.5 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 14.1, 18.0, 18.9, 22.6, 29.3, 29.41, 29.47, 29.5, 31.9, 34.0, 34.2, 180.1.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{13}H_{24}NaO_2$: 235.1669; found: 235.1661.

(+)-Grenadamide (*ent*-3)

DIPEA (421 mg, 540 μL, 3.26 mmol) and EDC (625 mg, 3.26 mmol) were added to a solution of acid *ent*-**5** (460 mg, 2.17 mmol), phenethylamine (**4**; 395 mg, 411 μL, 3.26 mmol) and 1-hydroxybenzotriazole (441 mg, 3.26 mmol) in CH_2Cl_2 (25 mL) at 0 °C. The reaction mixture was warmed to r.t. and stirred for 16 h. The reaction mixture was partitioned between aq HCl (0.1 M, 12 mL) and CH_2Cl_2 (12 mL). The organic layer was washed with sat. aq NH_4Cl (12 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Flash chromatography on silica gel (PE–EtOAc, 2:1) yielded (+)-grenadamide (*ent*-**3**).

Yield: 664 mg (2.11 mmol, 97%); colourless solid; mp 54.5–55.8 °C; $[\alpha]_D^{20}$ +12.6 (*c* 1.02, $CHCl_3$) [for (–)-grenadamide (**3**) Lit $[\alpha]_D$ –11.0 (*c* 0.1, $CHCl_3$)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.10–0.19 (m, 2 H), 0.30–0.44 (m, 2 H), 0.86 (t, *J* = 6.9 Hz, 3 H), 1.06–1.19 (m, 2 H), 1.21–1.32 (m, 10 H), 1.43–1.54 (m, 2 H), 2.20 (t, *J* = 7.6 Hz, 2 H), 2.80 (t, *J* = 7.0 Hz, 2 H), 3.49 (q, *J* = 6.9 Hz, 2 H), 5.74 (s, 1 H, NH), 7.13–7.25 (m, 3 H, Ph), 7.26–7.31 (m, 2 H, Ph).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 11.7, 14.0, 18.1, 18.8, 22.6, 29.3, 29.4, 29.6, 30.3, 31.8, 34.0, 35.6, 36.7, 40.5, 126.4, 128.5, 128.7, 138.8, 173.2.

HRMS (ESI+): *m*/*z* $[M + Na]^+$ calcd for $C_{21}H_{33}NaNO$: 338.2454; found: 338.2433.

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