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# An efficient asymmetric synthesis of grenadamide

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**Abstract**—The cyclopropane containing natural product grenadamide has been prepared in six steps using (*R*)-5,5-dimethyl-oxazolidin-2-one as a chiral auxiliary for asymmetric synthesis. Key synthetic steps include the use of the β-hydroxyl group of a *syn*-aldol product as a 'temporary' stereocentre to control the facial selectivity of a directed cyclopropanation reaction, as well as the use of phenylethylamine as a nucleophile for the direct aminolysis of an *N*-acyl-oxazolidin-2-one intermediate.


Grenadamide **1**, debromogrenadadiene **2** and grenadadiene **3** are natural products that were isolated from the marine cyanobacterium *Lyngbya majuscula*, by Sitachitta and Gerwick in 1998 (Fig. 1).[1] These structurally unique cyclopropyl fatty acid derived metabolites were shown to demonstrate cannabinoid receptor binding activity, as well as cytotoxicity towards cancer cells. Baird and co-workers subsequently confirmed the absolute configuration of the cyclopropane fragment of grenadamide **1** as (*R*,*R*) via total synthesis. Their synthesis required 14 steps, with an enzymatic desymmetrisation step being employed to introduce the stereogenic centres

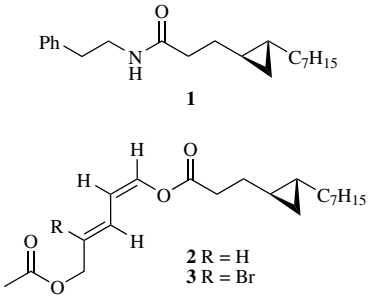


**Figure 1.** Structures of grenadamide **1**, debromogrenadadiene **2** and grenadadiene **3**.

of the cyclopropane fragment.[2] We thought that this approach appeared a little complicated since this structurally simple natural product contains only two stereogenic centres. Consequently, we now report an alternative asymmetric synthesis of grenadamide **1** in six steps from the chiral auxiliary (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **15**.

We are interested in developing novel synthetic strategies that employ 'temporary' stereogenic centres as stereodirecting groups to create remote stereocentres using substrate-directable reactions. For example, we have recently reported a three-step aldol/directed cyclo-propanation/*retro*-aldol protocol for the asymmetric synthesis of chiral cyclopropane carboxaldehydes in good ee (Fig. 2).[3] In this approach, a chiral auxiliary fragment **4** reacts with an α,β-unsaturated aldehyde **5** to afford a *syn*-aldol product **6** (Step 1), whose 'temporary' β-hydroxyl functionality is then used to control facial selectivity in a directed cyclopropanation reaction to afford cyclopropane **7** in very high de (Step 2). *retro*-Aldol cleavage of cyclopropane **7** results in destruction of the 'temporary' β-hydroxyl stereocentre, affording the chiral auxiliary fragment **4**, and the desired enantiopure cyclopropane carboxaldehyde **8** in high de (Step 3).

It was proposed that the excellent diastereoselectivity observed for cyclopropanation of *syn*-aldol **6** might also be exploited to devise a stereoselective synthesis of grenadamide **1** using the *retro*-synthetic analysis outlined in Figure 3. Therefore, grenadamide **1** would be prepared from conjugate reduction of α,β-unsaturated

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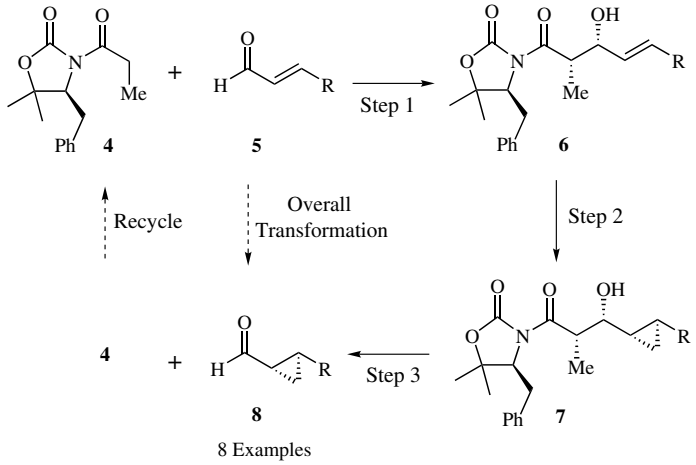



**Figure 2.** Aldol/cyclopropanation/*retro*-aldol strategy for the asymmetric synthesis of chiral cyclopropane carboxaldehydes.

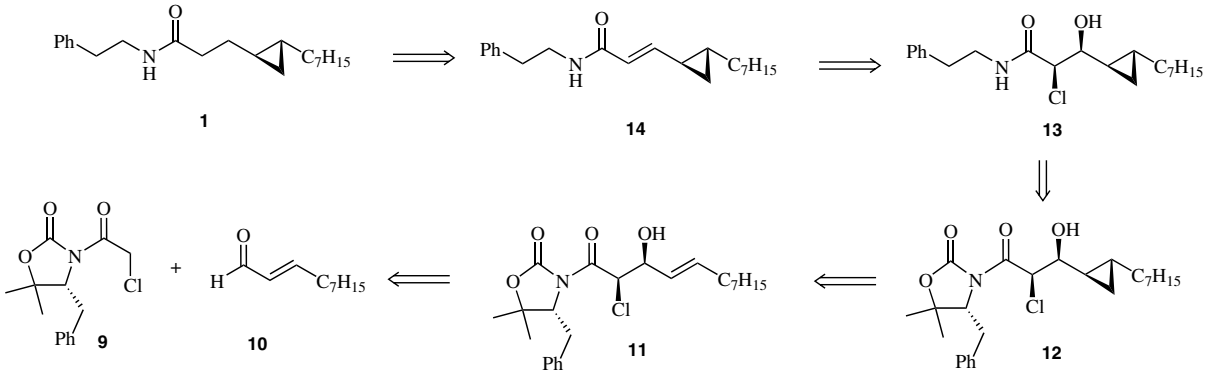
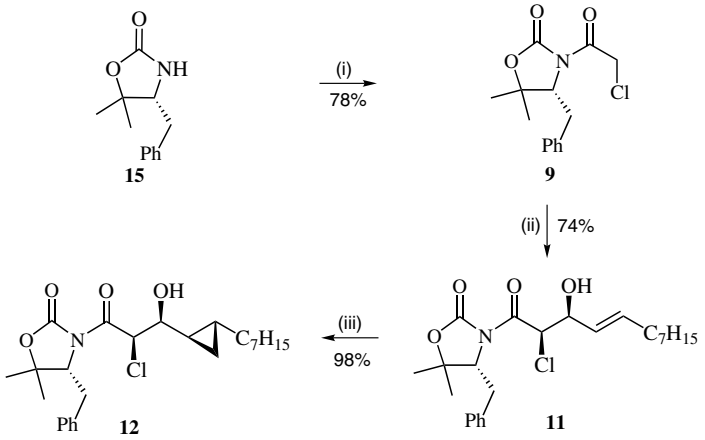



**Figure 3.** *retro*-Synthetic analysis of grenadamide **1**.

amide **14**, which could be derived from β-elimination of α-chloro-β-hydroxy-cyclopropane **13**.[4] The benzylamide functionality of cyclopropane **13** would be introduced via direct aminolysis of the oxazolidin-2-one fragment of **12** using phenylethylamine as a nucleophile. The cyclopropane ring of **12** could be introduced stereoselectively via a hydroxyl directed cyclopropanation reaction on *syn*-aldol **11** that would be prepared from aldol reaction of the (*Z*)-boron-enolate of *N*-chloroacetyl-5,5-dimethyl-oxazolidin-2-one **9** with (*E*)-dec-2-enal **10**. This synthetic strategy would therefore afford enantiopure grenadamide **1** in five steps from *N*-chloroacetyl-oxazolidin-2-one **9** via a relatively straightforward synthetic protocol that should be readily amenable to the preparation of analogues of this natural product as required.

It was thought necessary to employ the (*Z*)-boron enolate of *N*-chloroacetyloxazolidin-2-one **11** in order to ensure good levels of stereocontrol in the *syn*-aldol reaction, since boron enolates of *N*-acetyl-oxazolidin-2-ones are known to undergo aldol reactions in poor de.[5] It should be noted, however, that the presence of the α-chloro-substituent is essential for the subsequent β-elimination reaction of amide **13**, since it enables samarium diiodide to remove the β-hydroxyl functionality simultaneously, thus affording α,β-unsaturated amide **14** in a single step. It was decided to employ 'SuperQuat' oxazolidin-2-one **15** as a chiral auxiliary for this synthesis because the 5,5-dimethyl substituent would discourage nucleophilic attack of phenylethylamine at the endocyclic oxazolidin-2-one carbonyl of cyclopropane **12**, thus ensuring that this aminolysis reaction afforded amide **13** in good yield.[6]

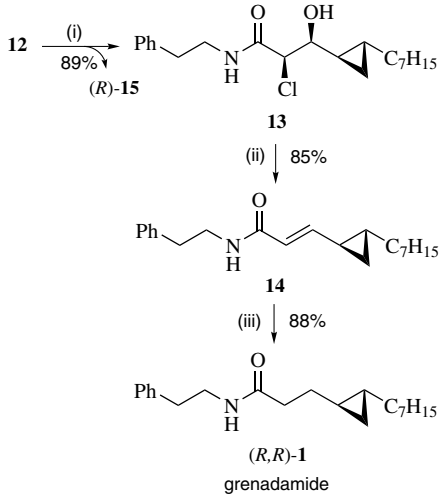
Our first task was to employ the *syn*-aldol/directed cyclopropanation methodology described in Figure 2 for the asymmetric synthesis of cyclopropane **12** in high de (Scheme 1). Therefore, (*R*)-4-benzyl-5,5-dimethyl-oxazolidin-2-one **15** was first prepared in 72% yield from unnatural D-phenylalanine using a previously reported procedure.[7] Treatment of (*R*)-**15** in THF at −78 °C with 1.1 equiv of *n*-BuLi, followed by addition of 1.1 equiv of chloroacetyl chloride gave α-chloroacetyl-oxazolidin-2-one **9** in 78% yield. Treatment of **9** with 1.1 equiv of 9-BBN-OTf and $^{i}Pr_2NEt$ in $CH_2Cl_2$ at 0 °C, followed by cooling to −78 °C and addition of (*E*)-dec-2-enal **10** resulted in *syn*-aldol **11** in 92% de, which was purified to >95% de in 74% yield via chromatography.[8] The *syn*-stereochemistry of aldol **11** was confirmed from the small $J_{(2',3')}$ coupling constant of 3.4 Hz observed in the $^1H$ NMR spectrum.[9] Reaction of *syn*-aldol **11** with 5 equiv of $Et_2Zn$ and $CH_2I_2$ in $CH_2Cl_2$ at −10 °C, resulted in a highly stereoselective cyclopropanation reaction, to afford *syn*-cyclopropyl aldol **12** in >95%




**Scheme 1.** Reagents and conditions: (i) 1.1 equiv *n*-BuLi, THF, −78 °C; chloroacetyl chloride; (ii) 1.1 equiv 9-BBN-OTF, $^{i}Pr_2NEt$, $CH_2Cl_2$, 0 °C; (*E*)-dec-2-enal **10**, −78 °C; (iii) 5 equiv $Et_2Zn$, $CH_2I_2$, $CH_2Cl_2$, −10 to 0 °C.

de and in 98% yield.[10] Cyclopropanations under this type of modified Furukawa conditions are normally *syn*-selective due to minimization of $A^{1,3}$ strain in the transition state, and as a consequence the absolute configuration of **12** was assigned accordingly.[11]

With the key cyclopropane **12**[12] in hand it was then necessary to transform it into grenadamide **1** by replacing the oxazolidin-2-one fragment with phenylethylamine, and substituting both the α-chloro and β-hydroxy substituents for hydrogen atoms (Scheme 2). It was found that simply dissolving cyclopropane **12** in neat phenylethylamine resulted in a clean aminolysis reaction to afford 5,5-dimethyl-oxazolidin-2-one (*R*)-**15** and amide **13**,[13] which was isolated in 89% yield after chromatographic purification.[14] Analysis of the $^1H$ NMR spectrum and TLC of the crude product of this aminolysis reaction revealed no evidence of any side products arising from a competing endocyclic cleavage pathway. Previous work by Concellòn et al. had shown that




**Scheme 2.** Reagents and conditions: (i) phenethylamine, 25 °C; (ii) 3 equiv $SmI_2$, THF, 25 °C; (iii) 0.2 equiv $CoCl_2$, MeOH/THF (2:1), 25 °C; 4 equiv $NaBH_4$, DMF.

treatment of α-halo-β-hydroxy-amides with 3 equiv of $SmI_2$ resulted in clean elimination reactions to afford (*E*)-α,β-unsaturated amides in high de.[15] Therefore, treatment of α-chloro-β-hydroxy-amide **13** with $SmI_2$ in THF at room temperature resulted in β-elimination to afford (*E*)-α,β-unsaturated amide **14**[16] in 85% yield. Analysis of the $^1H$ NMR spectrum of the crude reaction product revealed no evidence of any of its (*Z*)-isomer having been formed in this reaction. Finally, treatment of vinyl-cyclopropane **14** with $NaBH_4$ and 20 mol % of $CoCl_2$ in MeOH/THF,[17] resulted in conjugate reduction of its alkene functionality to afford grenadamide **1**[18] as a white crystalline solid in 88% yield. Comparison of the spectroscopic details with that reported previously for grenadamide (*R,R*)-**1** ($[\alpha]_D^{25}$ −11.0, (*c* 1.0, $CHCl_3$); Lit.[1] $[\alpha]_D^{25}$ −11.0 (*c* 0.1, $CHCl_3$)) revealed that the correct enantiomer of the natural product had been prepared in enantiopure form.

It should be noted that the synthetic strategy described for the synthesis of grenadamide **1** represents a powerful approach for the asymmetric synthesis of natural products that contain remote stereocentres. The strategy employed relies on the use of a chiral auxiliary to generate a 'temporary' stereocentre that then acts as a stereodirecting group to relay stereochemical information via a substrate-directable reaction. This approach is synthetically powerful because it has the potential to afford chiral products that contain new stereocentres which are remote to the chiral auxiliary fragment, creating chiral building blocks that are often difficult to access using conventional synthetic approaches. We anticipate that this new type of 'chiral relay' strategy will prove applicable to the combination of other types of chiral auxiliary and substrate-directable reactions, thus enabling the asymmetric synthesis of other classes of natural product that contain remote stereocentres.

In conclusion, we have demonstrated the asymmetric synthesis of grenadamide **1** in six steps from 5,5-dimethyl-oxazolidin-2-one **15** in an overall 38% yield. The use of this methodology is currently under investigation for the synthesis of debromogrenadadiene **2** and

grenadadiene **3**, since both these natural products should be available from the common intermediate **12**.

## Acknowledgements

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12. (*R*)-4-Benzyl-3-[(2′*R*,3′*S*)-2′-chloro-3′-((1″*R*,2″*R*)-2″-heptylcyclopropyl)-3′-hydroxy-propionyl]-5,5-dimethyl-oxazolidin-2-one **12**: $[\alpha]_D^{25}$ +11.0 (*c* 1.0, $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz): $\delta$ 0.40 (1H, m, *cyc*-C$H_2$), 0.61 (1H, m, *cyc*-C$H_2$), 0.79 (1H, m, *cyc*-C*H*), 0.85 (3H, t, *J* 6.8 Hz, C$H_3$), 0.90 (1H, m, *cyc*-C*H*), 1.12–1.29 (12H, m, C$H_2$), 1.32 (3H, s, C$H_3$), 1.36 (3H, s, C$H_3$), 2.61 (1H, br s, O*H*), 2.87 (1H, dd, *J* 14.3, 9.8 Hz, C$H_A$H$_B$Ph), 3.20 (1H, dd, *J* 14.3, 3.4 Hz, CH$_A$$H_B$Ph), 3.40 (1H, dd, *J* 7.9, 3.2 Hz, C*H*OH), 4.48 (1H, dd, *J* 9.8, 3.4 Hz, C*H*N), 5.78 (1H, d, *J* 3.2 Hz, C*H*Cl), 7.17–7.32 (5H, br m, Ar-*H*); $\delta_C$ ($CDCl_3$, 75 MHz): $\delta$ 10.8 ($CH_2$), 14.0 ($CH_3$), 16.6 (CH), 21.7 (CH), 22.3 ($CH_3$), 22.6 ($CH_2$), 28.6 ($CH_3$), 29.2 ($CH_2$), 29.3 ($CH_2$), 29.4 ($CH_2$), 31.8 ($CH_2$), 33.4 ($CH_2$), 34.6 ($CH_2$), 60.6 (CH), 64.2 (CH), 75.1 (CH), 83.0 (C), 126.9 (CH), 128.7 (CH), 129.0 (CH), 136.4 (C), 151.8 (C=O), 168.3 (C=O); $\nu_{max}$ (film)/$cm^{-1}$: 3500, 2924, 2854, 1770, 1716, 1605; MS ($ES^+$) 467.2668 ($[M+NH_4]^+$, $C_{25}H_{40}ClN_2O_4$ requires 467.2671).
13. (2*R*,3*S*)-2-Chloro-3-((1′*R*,2′*R*)-2-heptyl-cyclopropyl)-3-hydroxy-*N*-phenethyl-propionamide **13**: mp 64–65 °C; $[\alpha]_D^{25}$ −23.0 (*c* 1.0, $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz): $\delta$ 0.39 (1H, m, *cyc*-C$H_2$), 0.59 (1H, m, *cyc*-C$H_2$), 0.70 (1H, m, *cyc*-C*H*), 0.87 (3H, t, *J* 6.8 Hz, C$H_3$), 0.88 (1H, m, *cyc*-C*H*), 1.13–1.34 (12H, m, C$H_2$), 2.83 (2H, t, *J* 7.2 Hz, C$H_2$Ph), 3.49 (2H, m, NC$H_2$), 3.55 (1H, m, C*H*OH), 4.43 (1H, d, *J* 2.3 Hz, C*H*Cl), 6.77 (1H, br s, N*H*), 7.18–7.34 (5H, br m, Ar-*H*); $\delta_C$ ($CDCl_3$, 75 MHz): $\delta$ 11.3 ($CH_2$), 14.6 ($CH_3$), 17.2 (CH), 22.3 (CH), 23.0 ($CH_2$), 29.7 ($CH_2$), 29.8 (2 × $CH_2$), 32.2 ($CH_2$), 33.8 ($CH_2$), 35.8 ($CH_2$), 41.5 ($CH_2$), 64.9 (CH), 76.3 (CH), 127.0 (CH), 129.0 (CH), 129.2 (CH), 138.8 (C), 168.3 (C=O); $\nu_{max}$ (KBr)/$cm^{-1}$: 3277, 2921, 2856, 1647, 1557; MS ($ES^+$) 366.2198 ($[M+H]^+$, $C_{21}H_{33}ClNO_2$ requires 366.2194).
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16. (*E*)-3-((1*R*,2*R*)-2-Heptyl-cyclopropyl)-*N*-phenethyl-acrylamide **14**: mp 65–66 °C; $[\alpha]_D^{25}$ −37 (*c* 0.99, $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz): $\delta$ 0.67 (1H, m, *cyc*-C$H_2$), 0.75 (1H, m, *cyc*-C$H_2$), 0.87 (3H, t, *J* 7.2 Hz, C$H_3$), 0.94 (1H, m, *cyc*-C*H*), 1.17–1.40 (13H, br m, C$H_2$ and *cyc*-C*H*), 2.83 (2H, dd, *J* 6.8, 6.8 Hz, PhC$H_2$), 3.57 (2H, q, *J* 6.8 Hz, C$H_2$NH), 5.43 (1H, br s, N*H*), 5.71 (1H, d, *J* 15.0 Hz, C=*H*), 6.35 (1H, dd, *J* 15.0, 10.2 Hz, C=*H*), 7.16–7.34 (5H, br m, Ar-*H*); $\delta_C$ ($CDCl_3$, 75 MHz): $\delta$ 14.5 ($CH_3$), 15.9 ($CH_2$), 22.2 (CH), 23.0 ($CH_2$), 23.2 (CH), 29.6 ($CH_2$), 29.7 ($CH_2$), 29.8 ($CH_2$), 32.2 ($CH_2$), 34.0 ($CH_2$), 36.1 ($CH_2$), 40.9 ($CH_2$), 120.0 (CH), 126.8 (CH), 129.0 (CH), 129.2 (CH), 139.4 (C), 149.9 (CH), 166.5 (C=O); $\nu_{max}$ (KBr)/$cm^{-1}$: 3298, 2923, 2851, 1663, 1624, 1547; MS ($ES^+$) 314.2478 ($[M+H]^+$, $C_{21}H_{32}NO$ requires 314.2477).
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18. 3-((1′*R*,2′*R*)-2′-Heptyl-cyclopropan-1-yl)-*N*-phenethyl-propionamide (grenadamide) **1**: mp 46–47 °C; $[\alpha]_D^{25}$ −11.0 (*c* 1.0, $CHCl_3$) (Lit.[1] $[\alpha]_D^{25}$ −11.0, *c* 0.1, $CHCl_3$); $\delta_H$ ($CDCl_3$, 300 MHz): 0.16 (2H, m, *cyc*-C$H_2$), 0.38 (2H, m, 2 × *cyc*-C*H*), 0.87 (3H, t, *J* 6.8 Hz, C$H_3$), 1.14 (2H, m, C$H_2$), 1.24–1.33 (10H, m, C$H_2$), 1.49 (2H, m, C$H_2$), 2.18 (2H, t, *J* 7.5 Hz, C$H_2$CO), 2.81 (2H, t, *J* 6.8 Hz, PhC$H_2$), 3.52 (2H, q, *J* 6.8 Hz, C$H_2$NH), 5.51 (1H, br s, N*H*), 7.17–7.34 (5H, br m, Ar-C*H*); $\delta_C$ ($CDCl_3$, 75 MHz): 12.2 ($CH_2$), 14.5 ($CH_3$), 18.6 (CH), 19.3 (CH), 23.1 ($CH_2$), 29.8 ($CH_2$), 29.9 ($CH_2$), 30.0 ($CH_2$), 30.7 ($CH_2$), 32.3 ($CH_2$), 34.5 ($CH_2$), 36.1 ($CH_2$), 37.3 ($CH_2$), 40.9 ($CH_2$), 126.9 (CH), 129.0 (CH), 129.2 (CH), 139.3 (C), 173.5 (C=O); $\nu_{max}$ (KBr)/$cm^{-1}$: 3308, 2920, 2850, 1638, 1547; MS ($ES^+$) 316.2637 ($[M+H]^+$, $C_{21}H_{34}NO$ requires 316.2635).