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An efficient synthesis of semiplenamide C

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Abstract—Semiplenamides are anandamide-like fatty acid amide metabolites previously isolated from a marine cyanobacterium that display a range of biological activity. Novel *syn*-aldol/dehydration methodology has been developed for the stereoselective synthesis of the core (*E*)-α,β-unsaturated amide functionality of this class of natural product, and employed for the efficient synthesis of semiplenamide C.
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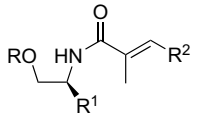
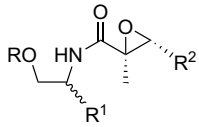
Marine cyanobacteria produce a wide range of bioactive and structurally complex natural products, a number of which have been shown to be derived from modified fatty acid fragments.[1] Gerwick and co-workers have recently reported the isolation of a series of novel semiplenamide metabolites from the marine cyanobacterium *Lyngbya semiplena* that were shown to be structurally related to anandamide fatty acid amides.[2] All of the semiplenamides A–G **1a**–**g** (Fig. 1) displayed toxicity toward the brine shrimp model system, semiplenamides A, B, and G exhibited weak affinity for the rat cannabinoid CB1 receptor, whilst semiplenamide A was a moderate inhibitor of the anandamide membrane transporter.[2] Given this range of biological activity, we were interested in developing efficient methodology for their stereoselective syntheses, and now report herein on the development of novel aldol/dehydration methodology for the efficient synthesis of semiplenamide C **1c**.



1a Semiplenamide A; R = H, R^1 = H, R^2 = (3*E*)-*n*-$C_{17}H_{33}$-
1b Semiplenamide B; R = Ac, R^1 = H, R^2 = (3*E*)-*n*-$C_{17}H_{33}$-
1c Semiplenamide C; R = H, R^1 = Me, R^2 = *n*-$C_{13}H_{27}$-
1d Semiplenamide D; R = Ac, R^1 = Me, R^2 = *n*-$C_{17}H_{35}$-
1e Semiplenamide E; R = Ac, R^1 = Me, R^2 = *n*-$C_{15}H_{31}$-



1f Semiplenamide F; R = H, R^1 = (*S*)-Me, R_2 = *n*-$C_{15}H_{31}$-
1g Semiplenamide G, R = Ac, R^1 = Me, R_2 = *n*-$C_{15}H_{31}$-

Figure 1. Structures of semiplenamides A–G **1a**–**g**.

We have recently reported that potassium alkoxides of β-hydroxy-*N*-acyloxazolidinones **2** undergo stereoselective elimination to afford trisubstituted (*E*)-α,β-unsaturated amides **5**.[3] In these elimination reactions, the potassium alkoxide of **2** first undergoes intramolecular attack at its oxazolidin-2-one carbonyl, resulting in *O*–*O* carbonyl migration, to afford an intermediate 1,3-oxazinane-2,4-dione alkoxide **3**. Subsequent anion equilibration affords enolate **4** that then undergoes stereoselective elimination of carbon dioxide to afford the trisubstituted secondary amide (*E*)-**5** (Fig. 2).[4]

This novel elimination methodology appeared ideally suited to the synthesis of the core fatty acid amide fragments of the semiplenamides A–E **1a**–**e** that we proposed could be easily prepared according to the retro-synthetic strategy described in Figure 3. Therefore, reaction between the enolate of an L-alanine derived *N*-acyloxazolidin-2-one with an appropriate aldehyde would afford a *syn*-aldol product, whose potassium alkoxide would subsequently undergo elimination to afford the desired (*E*)-amide functionality.

Keywords: *N*-Acyl-oxazolidin-2-one; *syn*-Aldol; Elimination; Natural product.
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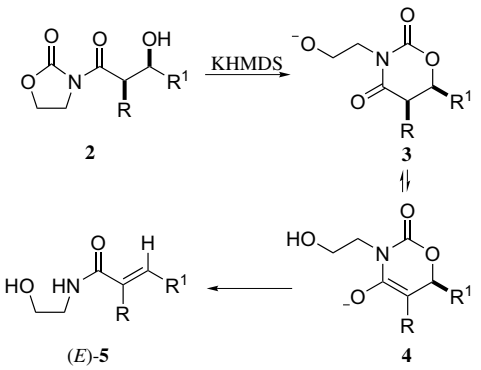


Figure 2. Intramolecular cyclization/elimination mechanism for formation of α,β-unsaturated amide (*E*)-**5**.

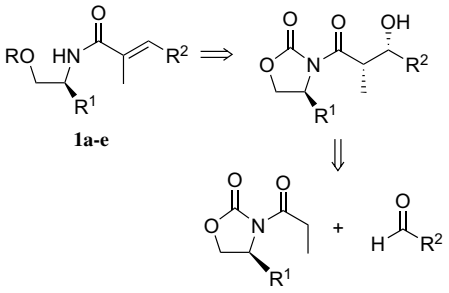
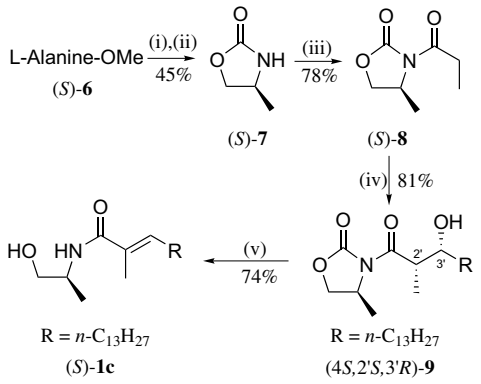


Figure 3. Retro-synthetic disconnection of semiplenamides A–E.



Scheme 1. Reagents and conditions: (i) $LiAlH_4$, Et_2O; (ii) $(EtO)_2CO$, KOEt, THF; (iii) *n*-BuLi, THF, −78 °C, EtCOCl; (iv) 9-BBN-OTf, $^iPr_2NEt$, CH_2Cl_2, 0 °C, *n*-$C_{13}H_{27}CHO$, −78 °C; (v) KO^{t}Bu, THF, −78 °C to rt.

Semiplenamide C **1c** was chosen as a representative synthetic target to develop this methodology, using L-alanine methyl ester (*S*)-**6** as an enantiopure starting material (Scheme 1). Reduction of (*S*)-**6** with $LiAlH_4$ in Et_2O, followed by treatment of the resultant (*S*)-amino-alcohol with diethyl carbonate under basic conditions, resulted in the formation of (*S*)-4-methyl-oxazolidin-2-one (*S*)-**7** in a 45% yield over two steps.[5] Subsequent treatment of (*S*)-**7** with *n*-BuLi in THF at −78 °C, followed by addition of propionyl chloride afforded *N*-propionyl-oxazolidin-2-one (*S*)-**8** in 78% yield.

Treatment of (*S*)-**8** with 1.1 equiv of 9-BBN-OTf and $^iPr_2NEt$ in CH_2Cl_2, followed by cooling to −78 °C, and addition of 1.1 equiv of tetradecanal,[6] resulted in *syn*-aldol **9** in >95% de, and in 81% yield after purification by chromatography.[7] The *syn*-stereochemistry of (4*S*,2′*S*,3′*R*)-aldol **9** was confirmed from the $J_{(2',3')}$ coupling constant of 3.0 Hz observed in its ^1H NMR spectrum.[8] The high levels of stereocontrol in this *syn*-aldol reaction are particularly noteworthy considering that facial selectivity is controlled by the sterically undemanding (4*S*)-methyl group of the oxazolidin-2-one fragment.

Generation of the potassium alkoxide of *syn*-aldol **9** via treatment with 1.1 equiv of KHMDS in toluene at 0 °C gave a low 23% yield of semiplenamide C (*S*)-**1c**, as well as *N*-propionyl-oxazolidin-2-one (*S*)-**8**, oxazolidin-2-one (*S*)-**7**, and tetradecanal as unwanted side-products arising from a competing retro-aldol cleavage pathway.[9] However, it was found that simply changing the base employed for deprotonation of *syn*-aldol **9** to KO^{t}Bu in THF at −78 °C resulted in a clean elimination reaction to afford semiplenamide C (*S*)-**1c** in 74% yield after purification by chromatography.[10]

In conclusion, we have developed efficient methodology for the synthesis of the core (*E*)-α,β-unsaturated amide fragments of semiplenamides A–E **1a**–**e**, and have applied this methodology to the first synthesis of semiplenamide C. Work is currently underway applying this approach to the stereoselective synthesis of the remaining semiplenamides, as well as for the synthesis of other natural and non-natural anandamide-like products.

Acknowledgements

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References and notes

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5. $[\alpha]_D$ for (*S*)-**8** = +15.5 (*c* 0.6, $CHCl_3$); lit. $[\alpha]_D$ for (*R*)-**8** = −8.1 (*c* 2.0, $CHCl_3$); Allali, H.; Tabti, B.; Alexandre, C.; Huet, F. *Tetrahedron: Asymmetry* **2004**, *15*, 1331.
6. These conditions have been used previously for asymmetric *syn*-aldol reactions using imidazolidin-2-one derived glycine enolates, see: Caddick, S.; Parr, N. J.; Pritchard, M. C. *Tetrahedron Lett.* **2000**, *41*, 5963.
7. Spectroscopic data for *syn*-aldol (4*S*,2′*S*,3′*R*)-**9**; $[\alpha]_D^{23} = +40.0$ (*c* 0.6, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz): 0.80 (3H, t, *J* = 7.0 Hz), 1.10 (3H, d,

J = 7.0 Hz), 1.20–1.30 (24H, m), 1.35 (3H, d, J = 7.0 Hz), 2.40 (1H, br s, OH); 3.68 (1H, qd, J = 7.0 and 3.0 Hz, $H_{2'}$), 3.86 (1H, m, $H_{3'}$), 3.94 (1H, dd, J = 8.0 and 3.0 Hz, H_{5A}), 4.38 (1H, app t, J = 8.0 Hz, H_{5B}), 4.52 (1H, m, H_4).

8. The $J_{(2',3')}$ coupling constant for *anti*-aldols of this type are normally >7.0 Hz; see: Feuillet, F. J. P.; Niyadurupola, G.; Green, R.; Cheeseman, M.; Bull, S. D. *Synlett* **2005**, 1090.
9. This type of retro-aldol pathway has been exploited previously for the asymmetric synthesis of enantiopure cyclopropane carboxaldehydes see: Cheeseman, M.; Feuillet, F. J. P.; Bull, S. D. *Chem. Commun.* **2005**, 2372.
10. $[\alpha]_D$ for (*S*)-**1c** = −8.3 (*c* 0.6, $CHCl_3$); lit. $[\alpha]_D$ −5.0 (*c* 0.3, $CHCl_3$); all other spectroscopic data for (*S*)-**1c** were identical to that published in Ref. 2.