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Total synthesis of arenamide A and its diastereomer

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This manuscript is dedicated to beloved teacher of G.P., Vennapusa Raja Reddy

ABSTRACT

Arenamide A and its diastereomer have been synthesized in a convergent fashion. The key steps involved in this synthesis are Sharpless asymmetric epoxidation, C–C bond formation, and macrolactamization.

The marine organisms continue to provide new chemicals as leads for better health care.[1] Recently, Fenical et al. reported the isolation, structure elucidation, and NFκB inhibition activities of three cyclic depsipeptides and named them as arenamides A–C from the extracts of *Salinispora arenicola* strain CNT-088.[2] These natural cyclic depsipeptides are characterized by 19-membered macrocycle with six subunits—Phe, Ala, Val, Gly, Leu, and 3-hydroxy-4-methyl decanoic acid (HMDA). The relative configuration of HMDA (at C-28, C-29) has been assigned '*syn*' based on NOE studies and absolute configuration was determined by Mosher ester data. The arenamides A and B blocked TNF induced activation in a dose and time dependent manner with IC_{50} values of 3.7 and 1.7 μM, respectively (Fig. 1).

Encouraged by these interesting properties coupled with our interest in total synthesis[3] of scarce, marine natural products, we embarked on the challenge of taking up an approach amicable for making diastereomers as well as analogues with ease. Herein, we report the first total synthesis of (28*R*,29*R*) arenamide A (**1**) and (28*S*,29*S*) arenamide A (**2**) using a stereoconvergent strategy.[4]

Retrosynthetically, arenamide A (**1** and **2**) (Scheme 1) can be obtained by the macrolactamization of the linear hexadepsipeptide **21/21a** which, in turn, could be prepared by coupling of the two key intermediates, the Phe-HMDA **20/20a** and the tetrapeptide component **15a.** The key HMDA segment was synthesized relying on Sharpless asymmetric epoxidation (SAE) wherein it was possible for us to synthesize both enantiomers (28*R*,29*R*) and (28*S*,29*S*) by simply changing from (−) DET to (+) DET, respectively, during epoxidation of **3**.

Thus, the known allyl alcohol **3**[5] was subjected to SAE[6] using (−) DET, $Ti(O^iPr)_4$, and *t*BHP followed by reductive opening with $NaCNBH_4$ catalyzed by $BF_3{\cdot}Et_2O$ furnished exclusively the 1,3-diol derivative **4**.[7,12] Selective tosylation of 1° alcohol (TsCl, NEt_3) and silylation of 2° alcohol (TBSOTf) were rather routine to yielded **5** in over 75% for two steps. A copper-mediated C–C bond formation[8] on tosylate **5** with pentyl magnesium bromide furnished **6** in 72% yield. This reaction in principle will allow one to synthesize other arenamides by simply changing the alkyl halides. The debenzylation[9] under Li–naphthalene provided alcohol **6a** which underwent a smooth oxidation[10] with TEMPO to carboxylic acid which was protected as *p*-nitro benzyl ester using *p*-nitro benzyl alcohol with EDC and DMAP furnished **7** in 97% yield. The desilylation[11] of **7** with HF–pyridine provided alcohol **8**[13] (Scheme 2), which is useful for coupling with the peptide part of the target. The ***ent*-8** (Scheme 2) was prepared by simply changing the SAE condition on allyl alcohol **3**.

With both enantiomers in hand, the further total synthesis of both isomers of arenamide A (**1** and **2**) has been taken up following a linear strategy (Schemes 3 and 4).

The tetrapeptide segment **15a** (Scheme 3) was synthesized from the commercially available protected (L)-amino acids. The condensation of Boc-Leu-OH **9** and alanine methyl ester **10** using EDC and HOB*t* as coupling reagents gave dipeptide (Boc-Leu-Ala-OMe) **11** in 82% yield. The Boc group of **11** was removed using TFA in CH_2Cl_2 resulting in amine **11a**, which was coupled with Cbz-Gly-Val-OH **14a** to yield tetrapeptide **15** in 64% yield. The dimer acid **14a** in turn was prepared by coupling of valine methyl ester **12** with Cbz-protected glycine **13** followed by hydrolysis using lithium hydroxide.

The saponification of ester functionality of tetrapeptide **15** using lithium hydroxide in THF and water (3:1) furnished tetrapeptide acid **15a.** The other partner Phe-HMDA **20/20a** was synthesized from HMDA **8/*ent*-8** by coupling with Boc-protected phenyl alanine (Boc-Phe-OH) **18** under EDC and DMAP conditions. Boc-Phe-HMDA **19/19a**, which was treated with TFA in CH_2Cl_2 gave free amine **20/20a** for further coupling with tetrapeptide **15a**. The

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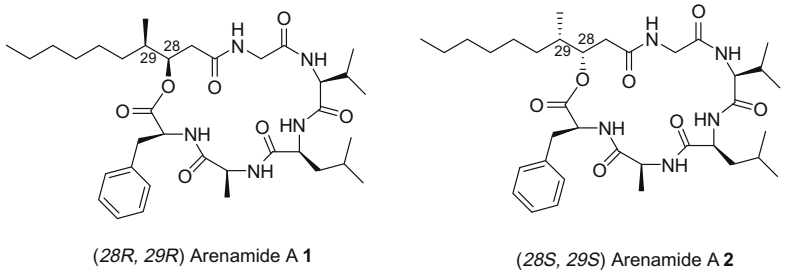
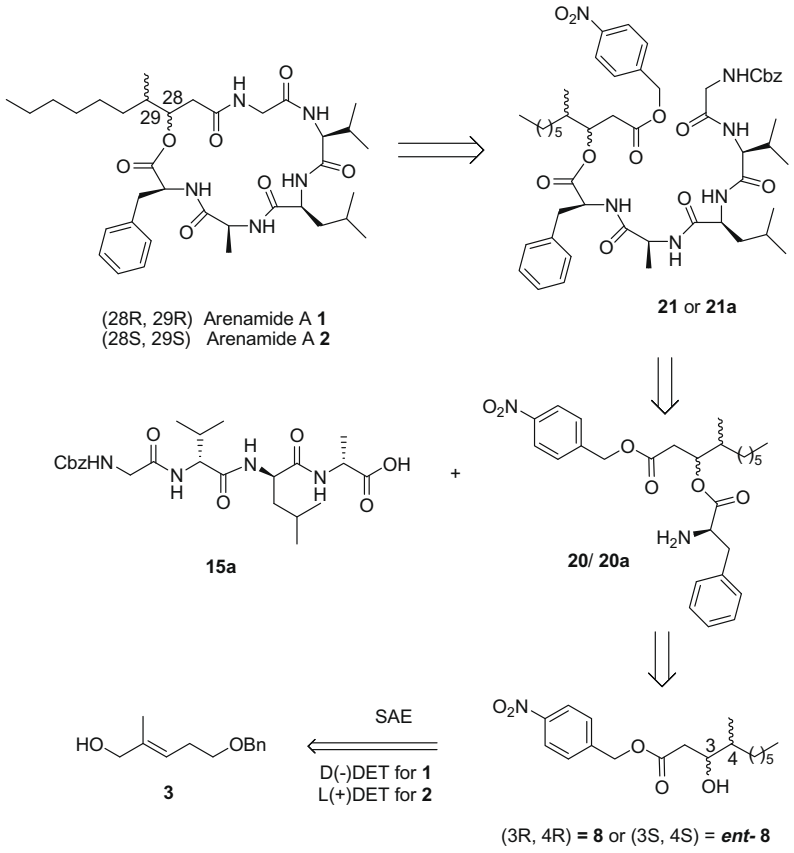
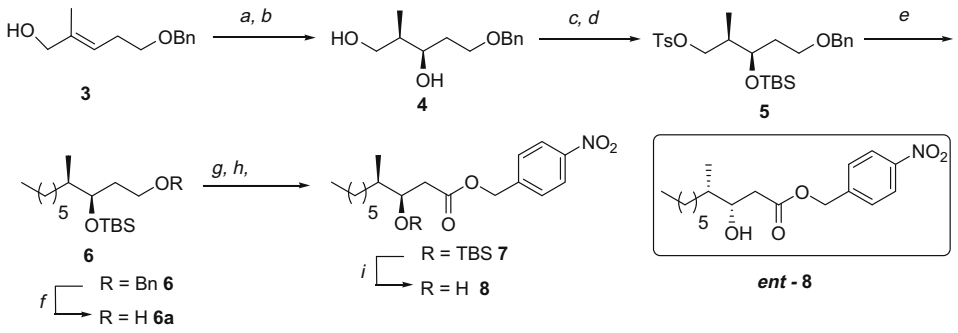


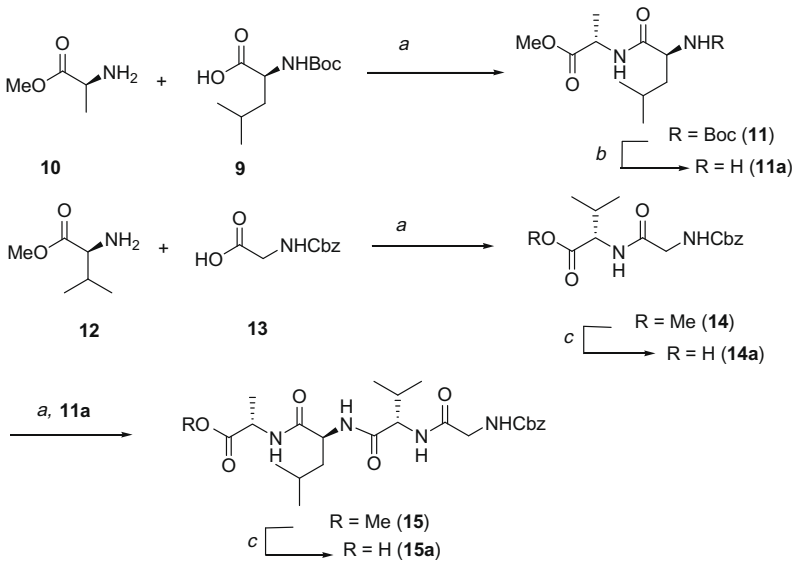
Figure 1. Structure of arenamides A **1** and **2**.



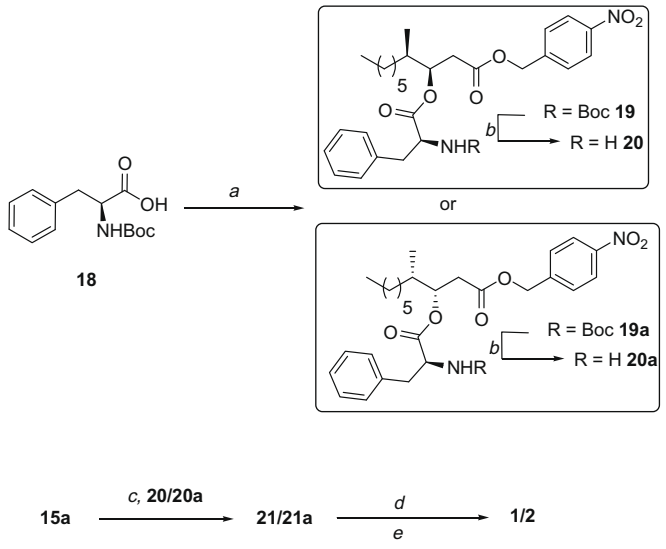
Scheme 1. Retrosynthetic analysis of arenamide A.



Scheme 2. Synthesis of HMDA derivative **8** and ***ent*-8.** Reagents and conditions: (a) $Ti(O^iPr)_4$, (−) DET, *t*BuOOH, CH_2Cl_2, −23 °C, 8 h, 82%; (b) $BF_3{\cdot}Et_2O$, $NaCNBH_4$, THF, 0 °C to reflux for 3 h, 64%; (c) Et_3N, *p*-TSCl, CH_2Cl_2, 0 °C to rt, 16 h, 78%; (d) Et_3N, TBSOTf, CH_2Cl_2, 0 °C, 30 min, quantitative; (e) $C_5H_{11}MgBr$, $CuBr{\cdot}Me_2S$, dry THF, −78 °C to rt, 12 h, 72%; (f) Li, naphthalene, dry THF, 0 °C, 10 min, 83%; (g) BAIB, TEMPO, CH_3CN:H_2O (1:1), rt, 7 h, 92%; (h) 4-$NO_2C_6H_4CH_2OH$, EDC, DMAP, 0 °C, 3 h, 97%; (i) HF–pyridine, THF, rt, 12 h, 88%.



Scheme 3. Synthesis of tetrapeptide segment **15a.** Reagents and conditions: (a) EDC, HOBt, DIPEA, CH_2Cl_2, 0 °C to rt 82% for **11**, 77% for **14**, 64% for **15**; (b) TFA, CH_2Cl_2, rt; and (c) LiOH, THF:H_2O (3:1), 0 °C.



Scheme 4. Synthesis of arenamides A (28*R*,29*R*) **1** and (28*S*,29*S*) **2**. Reagents and conditions: (a) EDC, DMAP, **8/*ent*-8**, CH_2Cl_2, 0 °C, 86%; (b) TFA, CH_2Cl_2, rt; (c) EDC, HOB*t*, DIPEA, CH_2Cl_2, 0 °C to rt, 74%; (d) Pd/C (10 mol %), H_2, IPA:THF (2.5:1); and (e) EDC, HOBt, DIPEA, CH_2Cl_2 (0.05×10^{-3} M), 0 °C to rt, 60% for **1**, 58% for **2** (for two steps).

tetrapeptide acid **15a** was coupled with amine **20/20a** under standard coupling conditions as mentioned above for amide bond formation to give hexadepsipeptide **21/21a** in good yield. Finally, deprotection of *p*-nitro benzyl and Cbz group by hydrogenation using Pd/C in isopropyl alcohol and THF mixture (3:2), followed by cyclization of linear hexadepsipeptide under high dilution (0.5×10^{-3} M) CH_2Cl_2 using EDC and HOB*t* as coupling reagents provided arenamide A **1/2**[14,15] (Scheme 4) in 60% yield.

The careful spectroscopic comparison of synthetic (28*R*,29 *R*) arenamide A (**1**) and (28*S*, 29*S*) arenamide A (**2**) with the reported natural product, clearly indicated that the natural product has (28*S*,29 *S*) configuration. Also the optical rotation of synthetic (28*S*,29*S*) isomer was closer to the reported natural product compared to (28*R*,29*R*) isomer.

In conclusion, the first total syntheses of (28*R*,29*R*) and (28*S*,29 *S*) diastereomers of arenamide A have been achieved and the spectroscopic data have been compared to provide insight into the correct stereochemistry of the natural product.

Acknowledgments

G.P.K. thanks UGC and K.S. thanks CSIR New Delhi for fellowship.

References and notes

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12. *Analytical and spectral data of compound* **4**: $[\alpha]_D^{30}$ −6.5 (*c* 1.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 7.40–7.27 (m, 5H), 4.53 (s, 2H), 4.03 (dt, *J* = 10.0, 2.2 Hz, 1H), 3,80–3.62 (m, 4H), 3.53 (br s, 1H), 3.0 (br s, 1H), 2.0–1.7 (m, 2H), 1.63 (m, 1H), 0.90 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 137.7, 128.4, 127.7, 127.6, 74.5, 73.3, 69.7, 66.5, 39.4, 32.8 and 10.8; EIMS: $[M+H]^+$ = 225.
13. *Analytical and spectral data of compound* **8**: $[\alpha]_D^{30}$ +19.5 (*c* 2.0 $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H), 5.25 (s, 2H), 3.99 (m, 1H), 2.59–2.49 (m, 3H), 1.60–1.39 (m, 1H), 1.39–1.06 (m, 10H), 0.92 (d, *J* = 6.1 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): 172.8, 147.6, 142.8, 128.3, 123.7, 71.2, 64.8, 38.8, 38.0, 32.6, 31.7, 29.4, 27.1, 22.6, 14.1 and 14.0; EIMS: $[M-H_2O+H]^+$ = 320.0; HRMS (ESI): calcd for $C_{18}H_{27}NO_5Na$ $[M+Na]^+$ = 360.1781, found: 360.1788.
14. *Analytical and spectral data of compound* **1**: $[\alpha]_D^{30}$ −43.0 (*c* 0.07 CH_3OH); ^1H NMR (600 MHz, DMSO-d_6): δ 8.16 (d, *J* = 7.3 Hz, 1H), 8.14 (d, *J* = 5.1 Hz, 1H), 7.87 (t, *J* = 5.8, 5.1 Hz, 1H), 7.79 (d, *J* = 7.1 Hz, 1H), 7.66 (d, *J* = 7.1 Hz, 1H), 7.33–7.12 (m, 5H), 5.09 (m, 1H), 4.39 (m, 1H), 4.06–3.90 (m, 4H), 3.85 (dd, *J* = 9.8, 5.8 Hz, 1H), 3.13 (dd, *J* = 14.3, 5.6 Hz, 1H), 2.96 (dd, *J* = 14.3, 8.3 Hz, 1H), 2.41 (m, 2H), 2.05 (m, 1H), 1.70–1.42 (m, 4H), 1.33–1.05 (m, 13H), 0.95–0.81 (m, 15H), 0.76 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): 171.6, 171.2, 170.8, 170.0, 169.8, 169.4, 138.3, 129.0, 128.2, 126.2, 75.2, 59.8, 54.2, 52.4, 48.8, 42.4, 40.0,

37.4, 36.3, 35.8, 31.3, 31.2, 28.9, 26.4, 24.3, 23.0, 22.1, 21.3, 19.2, 18.2, 17.6, 14.8, 14.1 and 13.9; White solid mp 239–240 °C; ESIMS: $[M+H]^+$ = 672.3; HRMS (ESI): calcd for $C_{36}H_{58}N_5O_7$ $[M+H]^+$ = 672.4331, found: 672.4336.

15. *Analytical and spectral data of compound* **2**: $[\alpha]_D^{30}$ −65.0 (*c* 0.09 CH_3OH); ^1H NMR (500 MHz, DMSO-d_6): δ 8.35 (d, *J* = 5.2 Hz, 1H), 8.09 (d, *J* = 9.4 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.70 (t, *J* = 5.2, 4.1 Hz, 1H), 7.29 (d, *J* = 7.3 Hz, 1H), 7.28–7.18 (m, 5H), 4.93 (dd, *J* = 9.4, 2.0 Hz, 1H), 4.29 (q, *J* = 13.6, 7.3 Hz, 1H), 4.27–4.09 (m, 3H), 3.92 (t, *J* = 8.3, 7.3 Hz, 1H), 3.69 (dd *J* = 16.8, 4.1 Hz, 1H), 2.92 (dq, *J* = 22.0, 15.7, 8.3 Hz, 1H), 2.57 (dd, *J* = 14.6, 9.4 Hz, 1H), 2.18 (d, *J* = 14.6 Hz, 1H), 1.93 (m, 1H), 1.60–1.49 (m, 3H), 1.45–1.35 (m, 1H), 1.29–1.09 (m, 13H), 0.94–0.77 (m, 15H), 0.52 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (200 MHz, DMSO-d_6): 171.6, 171.2, 171.0, 170.8, 169.4, 169.1, 136.6, 129.1, 128.4, 126.8, 75.2, 60.3, 54.8, 51.5, 47.5, 42.5, 40.0, 37.2, 36.5, 35.9, 31.4, 31.3, 29.8, 29.0, 26.4, 24.4, 23.3, 22.2, 20.7, 19.1, 19.0, 18.4, 14.5 and 13.9; White solid mp 228–230 °C; ESIMS: $[M+H]^+$ = 672.3; HRMS (ESI): calcd for $C_{36}H_{58}N_5O_7$ $[M+H]^+$ = 672.4331, found: 672.4336.