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Stereoselective formal total synthesis of the cyclodepsipeptide (−)-spongidepsin

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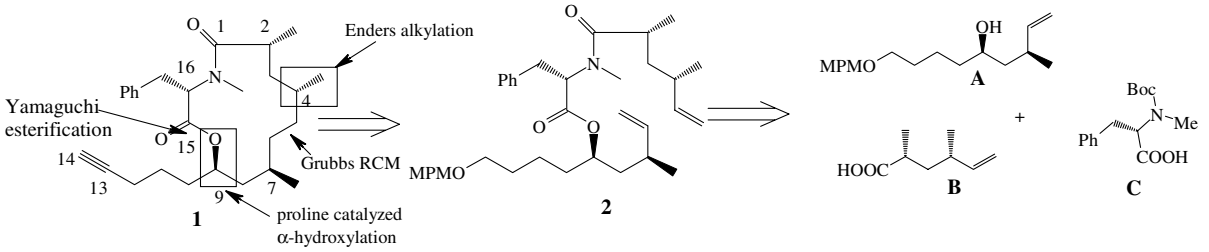
Abstract—The formal total synthesis of (−)-spongidepsin is achieved starting from easily available raw materials involving asymmetric α-hydroxylation, Enders alkylation, and RCM as key reactions.

Marine natural products continue to attract the attention of medicinal chemists owing to their fascinating structural diversity and complexity. (−)-Spongidepsin **1** is one such cyclodepsipeptide isolated from the sponge *Spongia* sp. collected from the waters off the Vanuatu Islands, Australia, by Riccio and associates.[1] This marine natural product encompasses a 13-membered ring containing five stereogenic centers. The absolute configuration of four of the five chiral centers were assigned by total syntheses[2,3] (three total syntheses have been reported to date),[2–4] whereas the *N*-methyl phenylalanine was identified as having the natural L-configuration during the isolation stage. Unfortunately, the limited resource[1] of **1** from Nature did not allow extensive screening for biological activity. The available data suggests **1** to be a potential anticancer compound.[1,5]

As outlined in our retrosynthetic analysis of **1** (Scheme 1), MacMillan α-hydroxylation of a (−)-citronellol derivative introduces the chirality[6] at C9, an Enders auxillary mediated enantioselective methylation at C4, Grubbs RCM to connect C5–C6 and Yamaguchi cyclization to build the macrocycle between C9 and C15 are the key steps. All these transformations were achieved with precision to build this scarce natural product. The key scaffolds viz. **A**, **B**, and **C** were prepared individually via high yielding reactions.

The construction of **A** began with commercially available (−)-citronellol **3** as the chiral synthon, which on protection of the primary alcohol as its silyl ether (TBDPSCl, imidazole, CH_2Cl_2, 0 °C to room temperature) followed by ozonolysis (O_3, CH_2Cl_2, −78 °C) provided hexanal derivative **4** (in a yield of 86% in two steps). The crucial MacMillan α-hydroxylation[6,7] on this substrate was achieved using nitrosobenzene and 40 mol % D-proline in DMSO, followed by rapid reduction with sodium borohydride to furnish the anilinoxy



Scheme 1. Retrosynthesis of (−)-spongidepsin.

Keywords: D-Proline; (−)-Citronellol; Roche ester; RCM; Enders auxillary; Phenyl alanine; Yamaguchi esterification.
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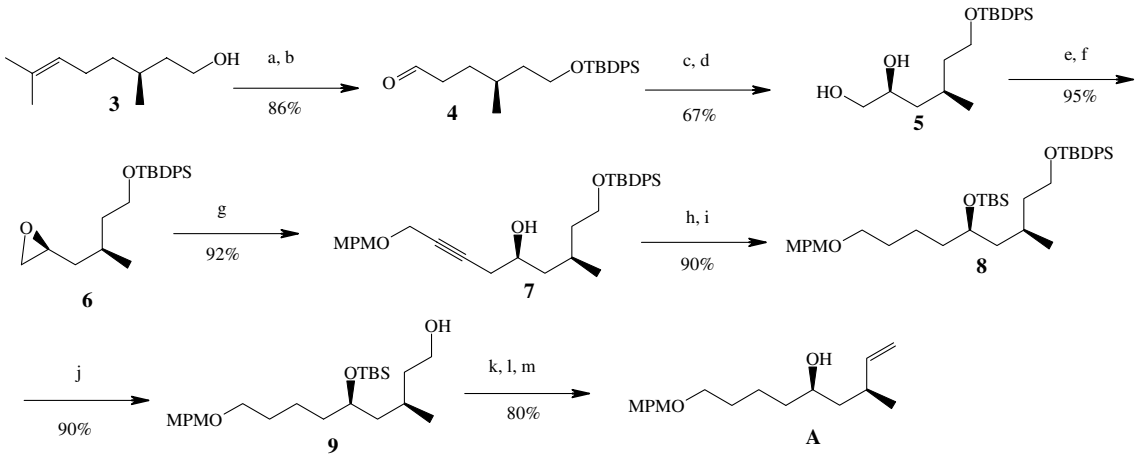
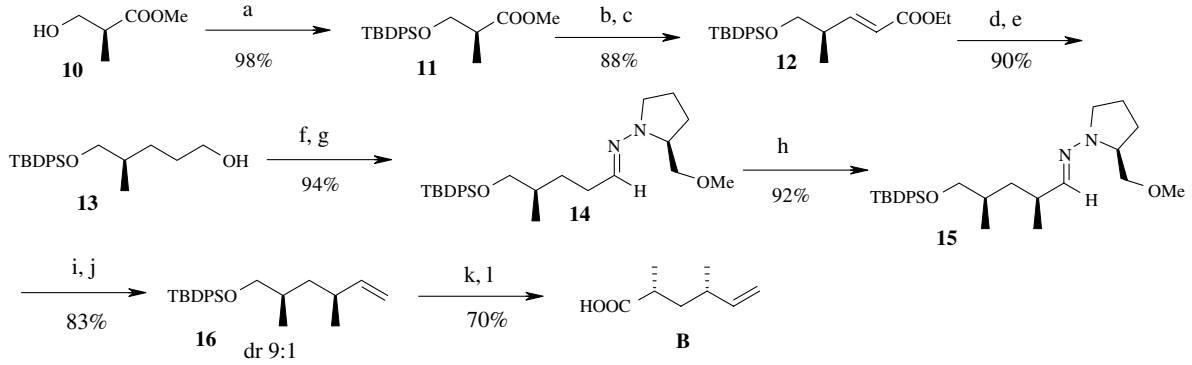
compound, which was further treated with 30 mol % $CuSO_4$ in methanol at room temperature to cleave the O–N bond to yield diol[7] **5** with high enantio and diastereoselectivity (67% yield, 98% ee, no traces of the other diastereomer could be detected by HPLC using a Chiralcel OB-H column, hexane, and isopropyl alcohol as eluents). The 1,2-diol functionality was converted to epoxide **6** in two steps with an overall yield of 95% (selective monotosylation followed by treatment with K_2CO_3, MeOH). This allowed chain extension via epoxide opening under $BF_3{\cdot}Et_2O$ catalysis with the propargyl anion of 4-methoxybenzyl protected propargyl alcohol [$HCCCH_2OCH_2C_6H_4(OCH_3)$] to give compound **7** with 100% regioselectivity. Exhaustive hydrogenation of the acetylenic functionality to saturation followed by hydroxyl protection (TBDMSCl, imidazole, CH_2Cl_2) gave fully and differentially protected triol **8**. Selective deprotection of the primary silyl ether (10 mol % NaOH, MeOH, reflux)[8] to give **9** was achieved in 90% yield. The precursor for RCM, **A** was realized in three more steps from **9** [(i) iodination (TPP, I_2, imidazole), (ii) KO^{t}Bu, THF, 0 °C followed by (iii) deprotection of the silyl ether (TBAF, THF)] in 80% overall yield (Scheme 2).

The other partner required for RCM was olefinic acid **B**, which was synthesized in a linear fashion (Scheme 3) starting from Roche ester **10**.[4] The standard silylation to give **11** was followed by homologation via DIBAL-H reduction and Wittig olefination to afford **12** in good yield, which underwent smooth reduction to alcohol **13** in two steps in 90% yield. The IBX mediated oxidation and hydrazone formation with Enders chiral auxillary (*S*)-1-amino-2-methoxymethylproline (SAMP) yielded **14** ready for stereoselective installation of a methyl group at C4. Thus, exposure of SAMP hydrazone[9] **14** to LDA at −100 °C followed by quenching with methyl iodide resulted in hydrazone **15** (dr = 9:1, 92% yield).[10] Ozonolysis of **15** followed by one carbon Wittig olefination (KO^{t}Bu, Ph_3PCH_3I) gave alkene **16.** Deprotection of the silyl ether using TBAF followed by oxidation (PDC, DMF) gave olefinic acid **B**. Synthon **C** required for the total synthesis of (−)-spongidepsin could be synthesized from natural phenylalanine using the reported procedure.[3]

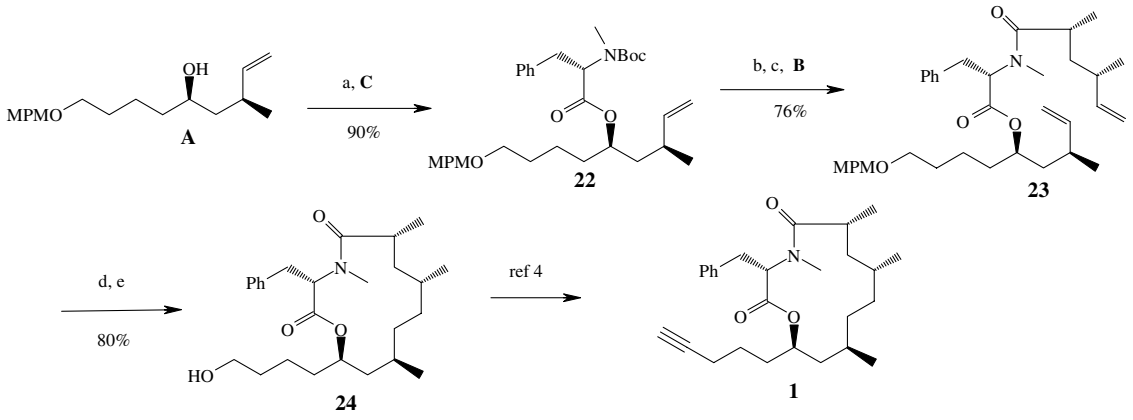
The synthesis of the target compound was successfully completed by combining these synthons in a seven step sequence as shown in Scheme 4. Synthon **A** was acylated



Scheme 2. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt, 1 h; (b) O_3, CH_2Cl_2, −78 °C, 15 min; (c) PhNO, D-proline (40 mol %), DMSO,rt, 30 min then $NaBH_4$, EtOH; (d) $CuSO_4$, MeOH, 12 h; (e) TsCl, NEt_3, Bu_2SnO, CH_2Cl_2, 3 h; (f) K_2CO_3, MeOH, 30 min; (g) $HCCCH_2OMPM$, *n*-BuLi, $BF_3{\cdot}OEt_2$, −78 °C; (h) Pd–$CaCO_3$, H_2, 10 h; (i) TBDMSCl, imidazole, CH_2Cl_2, rt, 5 h; (j) NaOH (10 mol % MeOH), reflux, 6 h; (k) TPP, I_2, imidazole ($Et_2O + CH_3CN$), 30 min; (l) KOBu^t, THF, 0 °C, 1 h; (m) TBAF, THF, rt, 2 h.



Scheme 3. Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, rt; (b) DIBAL-H, CH_2Cl_2, −78 °C; (c) $Ph_3PCHCOOEt$, C_6H_6; (d) DIBAL-H, CH_2Cl_2, 0 °C; (e) Pd–C, H_2, EtOAc; (f) IBX, (DMSO + THF); (g) SAMP, CH_2Cl_2, rt, 24 h; (h) LDA, CH_3I, −100 °C, Et_2O; (i) O_3, CH_2Cl_2, −78 °C; (j) KOBu^t, Ph_3PCH_3I, THF, 0 °C to −78 °C; (k) TBAF, THF, rt; (l) PDC, DMF, rt, 12 h.



Scheme 4. Reagents and conditions: (a) $Cl_3C_6H_2COCl$ (1.2 equiv), DIPEA (3 equiv), *N*-Me-*N*-Boc-Phe (1.1 equiv), THF; DMAP, toluene, 89%; (b) TBSOTf, 2,6-lutidine, TBAF, THF, rt; (c) EDCI, HOBt, CH_2Cl_2, then **B**; (d) Grubbs' II catalyst, CH_2Cl_2, reflux, 12 h; (e) Pd–C, H_2, EtOAc, 8 h.

with *N*-methyl-*N*-Boc-L-phenyl alanine **C** under Yamaguchi conditions to realize ester **22** in 90% yield.[11] This, on stepwise deprotection of the *N*-Boc group using TBSOTf, 2,6-lutidine and TBAF[12] and treatment with **B** in the presence of EDCI, HOBt provided the RCM precursor **23**. The ring closing metathesis of diene **23** was achieved using Grubbs' second generation catalyst[13] followed by palladium-catalyzed hydrogenation (Pd–C, EtOAc, H_2, 8 h) to give macrolactone **24** in 80% yield (two steps).[4] This late stage intermediate has been already converted to the target compound in two steps by Cossy and co-workers.[4] All the intermediate compounds including macrolactone **24** were fully characterized by IR, ^{1}HNMR, ^{13}C NMR, and mass spectral data.[14]

In summary, a formal total synthesis of (−)-spongidepsin has been achieved in a highly divergent and high yielding manner combining the 'chiron approach' and 'asymmetric synthesis' strategies. The key steps were organocatalyzed α-hydroxylation, α-methylation of an Enders intermediate, and Grubbs RCM.

Acknowledgments

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14. The spectral and physical data of macrolactone **24** matched in all respects with reported data (Ref. 4). Spectral and physical data for selected compounds, Compound **24**: colorless oil. $[\alpha]_D^{23}$ −186 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.32–7.22 (m, 3H), 7.21–7.15 (m, 2H), 5.16 (m, 1H), 3.67 (t, $J = 6.4$ Hz, 2H), 3.58–3.48 (m, 2H), 3.32–3.25 (m, 1H), 3.00–2.90 (m, 1H), 2.86 (s, 3H), 1.95–1.78 (m, 1H), 1.66–1.18 (m, 13H), 1.16–0.99 (m, 3H), 0.94 (d, $J = 7.1$ Hz, 3H), 0.91–0.78 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): 178.6, 170.2, 138.8, 129.5, 128.4, 126.5, 74.2, 65.2, 62.1, 41.3, 40.8, 37.4, 35.5, 34.3, 33.4, 32.6, 32.2, 32.4, 29.6, 28.3, 23.6, 23,4, 22.5, 21.7, 21.4, 18.8; IR (neat): ν_{max} 3434, 3027, 2925, 2854, 1735, 1632, 1452, 1275, 1213, 1076 cm^{-1}; HRMS (ESI): *m*/*z* 454.2941 (calcd for $C_{26}H_{41}NO_4Na$ 454.2933). Compound **A**: colorless oil. $[\alpha]_D^{23}$ +4.0 (*c* 1.1, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.26 (d, $J = 9.2$ Hz, 2H), 6.87 (d, $J = 9.2$ Hz, 2H), 5.90–5.60 (m, 1H), 5.12–5.84 (m, 2H), 4.43 (s, 2H), 3.80 (s, 3H), 3.75–3.59 (m, 1H), 3.45 (t, $J = 5.8$ Hz, 2H), 2.43–2.22 (m, 1H), 1.80–1.2 (m, 8H), 1.00 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 159.3, 145.3, 130.9, 129.4, 114.0, 113.1, 72.8, 70.4, 70.1, 55.4, 44.7, 37.7, 35.7, 29.9, 26.2, 22.5, 20.5, 18.4; IR (neat): ν_{max} 3425, 2929, 2860, 1612, 1512, 1246, 1096 cm^{-1}; LC–MS: *m*/*z* 293 (M+H$^+$). Compound **15**: colorless oil. $[\alpha]_D^{23}$ −62.9 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.63 (m, 4H), 7.42–7.30 (m, 6H), 6.38 (d, $J = 6.0$ Hz, 1H), 3.56–3.42 (m, 3H), 3.38 –3.20 (m,

5H), 2.73–2.58 (m, 1H), 2.44–2.29 (m, 1H), 2.00–1.81 (m, 2H), 1.80–1.67 (m, 2H), 1.49–1.37 (m, 2H), 1.32–1.17 (m, 2H), 1.05 (s, 9H), 0.99 (d, $J = 6.8$ Hz, 3H), 0.93 (d, $J = 6.8$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): 144.5, 135.5, 134.1, 129.3, 127.6, 74.7, 68.7, 63.5, 59.1, 50.2, 38.8, 34.7, 33.2, 27.0, 26.5, 22.0, 19.3, 18.9, 17.0; IR (neat): ν_{max} 3425, 2929, 2860, 1612, 1512, 1246, 1096 cm^{-1}. HRMS (ESI): m/z ($M+H^+$) 481.3264 (calcd for $C_{29}H_{45}N_2O_2Si$ 481.3250). Compound **5**: colorless oil. $[\alpha]_D^{23}$ −5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$):δ 7.69–7.57 (m, 4H), 7.42–7.27 (m, 6H), 3.79–3.61 (m, 3H), 3.59–3.43 (m, 1H), 3.40 –3.23 (m, 1H), 2.78–2.46 (br s, 2H), 2.01–1.21 (m, 4H), 1.19–1.09 (m, 1H), 1.05 (s, 9H), 0.87 (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): 136.3, 133.5, 129.3, 127.5, 70.6, 66.8, 61.3, 40.2, 39.5, 27.3, 26.7, 20.4, 19.5. IR (neat): ν_{max} 3416, 1617, 1350, 1110, 795, 745 cm^{-1}. HRMS (ESI): m/z 409.2166 (calcd for $C_{23}H_{34}O_3NaSi$ 409.2174).