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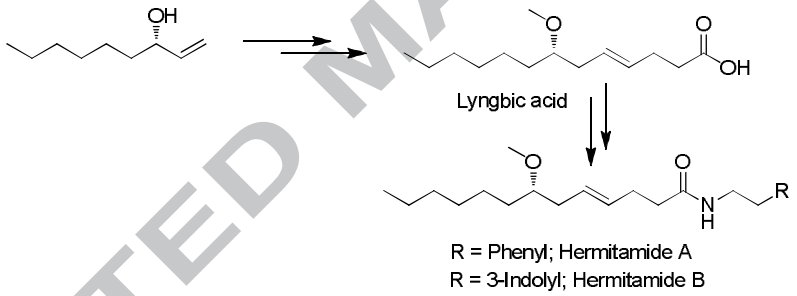

Graphical Abstract

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A concise total synthesis of lyngbic acid, hermitamides A and B

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Abstract: A concise total syntheses of lyngbic acid, hermitamides A and B have been accomplished in a highly enantioselective manner involving CBS asymmetric reduction, hydroboration and stereospecific Julia-Lythgoe olefination.

Keywords: Hermitamides, marine natural products, CBS asymmetric reduction, hydroboration, Julia-Lythgoe olefination

Hermitamides A and B are lipopeptides that were isolated from *Lyngbya majuscula* cyanobacteria.[1] Lyngbic acid was also isolated from the marine cyanophyte Lyngbya majuscule (Figure 1).[2] They act as sodium channel blockers[3] and also exhibit important biological activities such as immunosuppressive activity (ED_{50} 6 µg/mL on culture cells with concanavaline K and LPS). Hermitamides A (**1**) and B (**2**) also display IC_{50} values of 2.2 μM and 5.5 μM against Neuro-2a neuroblastoma cells in tissue culture.

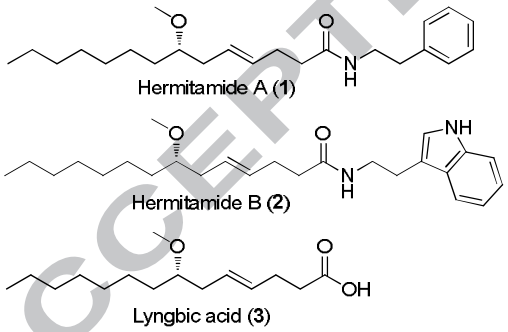
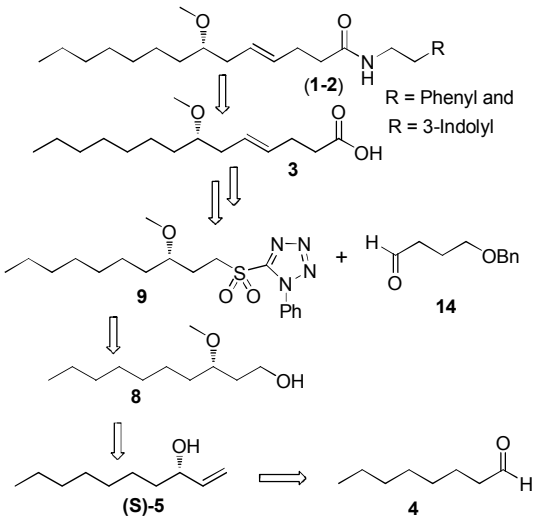


Figure 1. Natural products from *L. majuscula* cyanobacteria

As a result, a racemic synthesis of hermitamides A and B has been reported using ruthenium catalyzed cross-metathesis reaction as a key step to install the alkene fragment.[4] Subsequently, enantioselective synthesis of lyngbic acid has been accomplished by various approaches such as the ring-opening of chiral epoxide,[5] lipase mediated kinetic resolution,[6] and asymmetric allylation of the requisite aldehyde.[7] In addition, a rhodium catalyzed conjugate addition of chiral potassium trifluoroalkenylborate has been employed to construct the side chain of hermitamides.[8] Recently, Sharpless asymmetric epoxidation has successfully been used in the synthesis of novel malyngamide derivatives.[9] Keck allylation and the stereospecific formation of *E*-olefin by Johnson–Claisen rearrangement have been utilized to accomplish the total synthesis of hermitamides A (**1**) and B (**2**).[3]

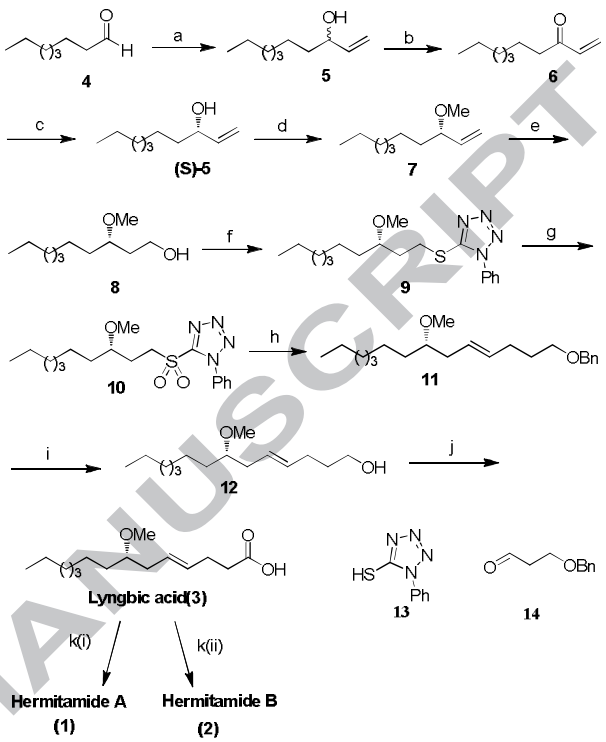
In this article, we wish to report a short and efficient enantioselective synthesis of hermitamide natural products employing CBS reduction, hydroboration and Julia-Lythgoe olefination as key steps. The retrosynthesis of hermitamide A (**1**) and B (**2**) and lyngbic acid **3** is illustrated in Scheme 1. 7-Methoxytetradec-4-enoic acid **3** is a common structural unit in both natural products. Therefore, we proposed the synthesis of 7-methoxytetradec-4-enoic acid to be achieved by the Julia-Lythgoe olefination strategy. Hermitamides A (**1**) and B (**2**) could be cleaved into two main fragments, i.e. alkyl sulfone **10** and aldehyde **14**. Chiral alkyl sulfone **10** could be conveniently prepared from the methoxy alcohol **8**. The chiral center of the key intermediate **10** can be generated from the CBS reduction of **6**, followed by methylation of the hydroxyl group and subsequent hydroboration of the terminal olefin. Compound **6** could easily be obtained from *n*-octanal **4** through vinylation followed by oxidation of the allylic alcohol **5**.



Scheme 1. Retrosynthesis of hermitamides A and B

Synthesis of hermitamides A (**1**) and B (**2**) are depicted in Scheme 1 commenced from *n*-octanal. Vinylation of *n*-octanal **4** with vinyl magnesium bromide gave the allylic alcohol **5** in 92% yield. Oxidation of the secondary allylic alcohol **5** with IBX in DMSO afforded the enone **6** in 96% yield. Asymmetric reduction of the ketone **6** using CBS catalyst gave the chiral allylic alcohol (*S*)-**5** in 80% yield with high enantiomeric excess (>99%).[10] Methylation of (*S*)-**5** using Meerwein's reagent (Me_3OBF_4) in DCM at 0 °C to room temperature furnished the compound **7** in 80%. Hydroboration of the terminal olefin in compound **7** using BH_3.DMS in THF followed by oxidation with hydrogen peroxide afforded the primary alcohol **8** in 83% yield.[11] Conversion of alcohol **8** into aryl sulfide **9** was achieved using TPP/DIAD and 1-phenyltetrazole-5-thiol under Mitsunobu conditions.[12] Oxidation of the aryl sulfide **9** using ammonium molybdate and hydrogen peroxide gave the sulfone **10** in 85% yield over two steps.[12] Having both the aldehyde **14** and sulfone **9** in hand, we then attempted Julia-Lythgoe olefination[12,13] using KHMDS at -78 °C. The corresponding olefin **11** was obtained in 83% yield with *E*-geometry exclusively. Debenzylation of **11** with Li/naphthalene in THF gave the primary alcohol **12**, which was then subjected to oxidation with DMP followed by $NaClO_2$ to furnish the lyngbic acid in 94% yield over two steps.[14]

Once lyngbic acid **3** was in hand, we carried out the synthesis of hermitamides A (**1**) and B (**2**). Therefore, the coupling of **3** with different amines like 2-phenylethyl amine and 3-indolylethyl amine using EDCI and HOBt in DCM gave **1** and **2** in good yields as presented in Scheme 2.



Scheme 2: *Reagents and conditions*: (a) vinyl magnesium bromide, THF, 0 °C, 3h, 92%; (b) IBX, DMSO, r.t., 3 h; 96%; (c) *R*-CBS catalyst, THF, -40 °C, BH_3. DMS, 3 h, 80%, (dr 95:5); (d) Me_3OBF_4, proton spong, CH_2Cl_2, 0 °C to r.t., 2 h, 80%; (e) (i) BH_3. DMS, THF, 5h, 0 °C, (ii) H_2O_2, NaOH, H_2O, 3h, 83%. (f) **13**, Ph_3P, DIAD, THF, -20 °C; (g) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, 30% H_2O_2, EtOH, r.t., (85%, two steps); (h) **14**, KHMDS, THF, –78 °C, 16 h, 83%; (i) Li, naphthalene, THF, -20 °C, 90%; (j) (i) DMP, CH_2Cl_2, r.t.; (ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, ^{t}BuOH, H_2O, r.t. (94%, two steps); (k) (i)2-phenylethyl amine, EDCI, HOBt, DIPEA, DCM, 0 °C to r.t., 10 h, 77%, (ii) 3-indolylethyl amine, EDCI, HOBt, DIPEA, DCM, 0 °C to r.t., 10 h, 75%.

In conclusion, we have developed an efficient approach for the synthesis of lyngbic acid, hermitamides A and B starting from *n*-octanal. The key steps involved in this synthesis are Grignard reaction, CBS asymmetric reduction, hydroboration and Julia-Lythgoe olefination. Chiral alkoxy alcohol **8** was constructed from the allyl alcohol (*S*)-**5**, which in turn was derived from *n*-octanal. Coupling of alkyl sulfone **10** with aldehyde **14** *via* Julia-Lythgoe olefination provides the corresponding *E*-olefin exclusively. The present synthetic approach involves 10 steps from *n*-octanal with 22.% overall yield of

hermitamides A and 21% overall yield of hermitamides B.

Acknowledgements

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14. (*S*)-Dec-1-en-3-ol (**5**): ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, *J* = 7.0 Hz, 3H), 1.23 - 1.34 (m, 10H), 1.46 - 1.56 (m, 2H), 4.10 (q, *J* = 6.9, 12.9 Hz, 1H), 5.10 (dt, *J* = 10.4, 1.4 Hz, 1H), 5.22 (dt, *J* = 17.2, 1.4 Hz, 1H), 5.87 (ddd, *J* = 17.1, 10.5, 6.4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.3, 114.5, 73.3, 37.0, 31.8, 29.5, 29.2, 25.3, 22.6, 14.1. IR (KBr): υ 3437, 2954, 2924, 2854, 1631, 1091, 918 cm^{-1}; MS (ESI) *m/z* for $C_{10}H_{20}O$ $[M+H]^+$ 157; $[\alpha]_D^{20}$ +8.2 (*c* 0.3, $CHCl_3$) . [Lit.[10] $[\alpha]_D^{20}$ +8.2 (*c*, 1.2, $CHCl_3$)].

(*S*)-3-Methoxydec-1-ene (**7**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (t, *J* = 7.6 Hz, 3H), 1.20 - 1.31 (m, 10H), 1.42 - 1.52 (m, 2H), 3.27 (s, 3H), 3.49 (q, *J* = 6.8, 14.4 Hz, 1H), 5.16 (d, *J* = 9.1 Hz, 1H), 5.20 (m, 1H), 5.64 (ddd, *J* = 16.6, 9.1, 6.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.9, 116.9, 83.1, 56.1, 35.3, 31.8, 29.6, 29.2, 25.3, 22.6, 14.1. IR (KBr): υ 2924, 2854, 1598, 1552, 1441, 1049, 798 cm^{-1}; MS (ESI) *m/z* for $C_{11}H_{22}O$ $[M+H]^+$ 171; $[\alpha]_D^{20}$ +6.25 (*c*, 0.4, $CHCl_3$).

(*S*)-3-Methoxydecan-1-ol (**8**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.77 (m, 2H), 3.41 (m, 1H), 3.36 (s, 3H), 2.62 (brs, 1H), 1.88-1.55 (m, 2H) 1.48 (m, 2H), 1.37-1.22 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.2, 61.1, 56.3, 35.3, 32.8, 31.7, 29.7, 29.1, 24.9, 22.6, 14.0; IR (KBr): υ 2927, 2855, 1463, 1376, 1135, 1093, 1054, 772, 722 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{11}H_{25}O_2$ $[M+H]^+$ 188.1776, found 188.1773; $[\alpha]_D^{20}$ +15.8 (*c* 1.2, $CHCl_3$).

(*S*)-5-((3-Methoxydecyl)sulfonyl)-1-phenyl-1*H*-tetrazole (**10**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.70 (m, 2H), 7.62 (m, 3H), 3.82 (m, 2H), 3.36 (m, 1H), 3.33 (s, 3H), 2.22 (m, 1H), 2.03 (m, 12H), 1.48-1.37 (m, 2H), 1.35-1.23 (m, 10H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.4, 131.4, 129.6, 125.03, 78.2, 56.4, 52.5, 32.8, 31.7, 29.5, 29.1, 25.8, 24.9, 22.5, 14.0; IR (KBr): υ 2925, 2853, 1598, 1499, 1463, 1340, 1157, 1092, 1013, 869, 765 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{18}H_{29}O_3N_4S$ $[M+H]^+$ 381.1961, found 381.1954; $[\alpha]_D^{20}$ +10.9 (*c* 1.9, $CHCl_3$).

(7*S*,4*E*)-(((Methoxytetradec-en-1-yl)oxy)methyl) benzene (**11**): ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (m, 2H), 7.33 (m, 2H), 5.44 (q, *J* = 5.8, 12.4 Hz, 2H), 4.50 (s, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.32 (s, 3H), 3.13 (q, *J* = 5.7, 11.5 Hz, 1H), 2.18 (q, *J* = 5.6, 11.2 Hz, 2H), 2.10 (q, *J* = 7.7, 14.3 Hz, 2H), 1.69 (q, *J* = 7.7, 14.3 Hz, 2H), 1.46-1.39 (m, 2H), 1.35-1.22 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 131.9, 128.3, 127.5, 127.4, 126.3, 80.8, 72.8, 69.7, 56.4, 36.3, 33.3, 31.8, 29.7, 29.5, 29.2, 25.2, 22.6, 14.08; IR (KBr): υ 2924, 2853, 1633, 1458, 1376, 1218, 968, 771 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{22}H_{37}O_2$ $[M+H]^+$ 333.2786, found: 333.2785; $[\alpha]_D^{20}$ -10.6 (*c* 0.3, $CHCl_3$).

(7*S*,4*E*)-Methoxytetradec-en-1-ol (**12**): ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.47 (m, 2H), 3.66 (t, *J* = 5.2 Hz, 2H), 3.32 (s, 3H), 3.13 (m, 1H), 2.20 (t, *J* = 5.7 Hz, 2H), 2.11 (q, *J* = 7.1, 12.9 Hz, 2H), 1.69-1.52 (m, 4H), 1.30-1.24 (m, 10H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.1, 126.8,

80.8, 62.5, 56.4, 36.3, 33.3, 32.9, 31.8, 30.0, 29.7, 29.3, 29.2, 22.6, 14.1; IR (KBr): υ 3026, 2929, 2857, 1634, 1455, 1375, 1056, 971, 784 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{30}O_2Na$ $[M+Na]^+$ 265.2245, found: 265.2237; $[\alpha]_D^{20}$ - 7.3 (*c* 0.5, $CHCl_3$).

(7*S*,4*E*)-Methoxytetradecenoic acid (**3**): ^1H NMR (300 MHz, $CDCl_3$): δ 5.48 (m, 2H), 3.33 (s, 3H), 3.16 (quin, *J* = 6.0, 5.2, 12.0 Hz, 1H), 2.41 (d, *J* = 6.0 Hz, 2H), 2.35 (m, 2H), 2.20 (t, *J* = 4.5 Hz, 2H), 1.46-1.40 (m, 2H), 1.34-1.23 (m, 10H), 0.89 (t, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.75, 130.1, 127.7, 80.7, 56.4, 36.2, 33.8, 33.2, 31.8, 29.6, 29.2, 27.6, 25.2, 22.6, 14.0; IR (KBr): υ 2927, 2856, 1711, 1458, 1372, 1190, 1096, 970, 768 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{15}H_{29}O_3$ $[M+H]^+$ 257.2113, found: 257.2111; $[\alpha]_D^{20}$ -10.8 (*c* 1.4, $CHCl_3$). Lit.[1] $[\alpha]_D^{26}$ -11.1 (*c*, 3.9, $CHCl_3$).

2-(1*H*-Indol-3-yl)-ethyl-(7*S*,4*E*)-methoxytetradecen amide (**2**): ^1H NMR (300 MHz, $CDCl_3$): δ 8.11 (brs, 1H), 7.60 (d, *J* = 8.3 Hz, 1H), 7.39 (d, *J* = 8.3 Hz, 1H), 7.22 (t, *J* = 8.3 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 7.04 (d, *J* = 2.2 Hz, 1H) 5.55 (brs, 1H), 5.43 (m, 2H), 3.61 (q, *J* = 6.0, 12.8 Hz, 2H), 3.31 (s, 3H), 3.13 (t, *J* = 6.0 Hz, 1H), 2.98 (t, *J* = 6.7 Hz, 2H), 2.37-2.26 (m, 2H), 2.20-2.14 (m, 4H), 1.45-1.38 (m, 2H), 1.33-1.22 (m, 10H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.39, 136.4, 130.8, 127.4, 122.1, 121.9, 119.4, 118.6, 115.2, 112.9, 111.2, 80.6, 56.4, 39.5, 36.5, 36.2, 33.4, 33.2, 31.7, 29.7, 29.2, 28.5, 25.2, 22.6, 14.0; IR (KBr): υ 2926, 2854, 1647, 1544, 1456, 1358, 1222, 1094, 970, 771, 742 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{25}H_{39}O_2N_2$ $[M+H]^+$ 399.3005, found: 399.3006; $[\alpha]_D^{20}$ –4.2 (*c* 0.65, $CHCl_3$). Lit.[1] $[\alpha]_D^{26}$ –4.5 (*c*, 0.10, $CHCl_3$).

Phenethyl-(7*S*,4*E*)-methoxytetradecenamide (**1**): ^1H NMR (500 MHz, $CDCl_3$): δ 7.31(t, j = 7.2 Hz, 2H), 7.24 (t, j = 6.9 Hz, 1H), 7.19(d, j = 6.9 Hz, 2H), 5.53 (brs, 1H), 5.44 (m, 2H), 3.52 (q, *J* = 6.7 Hz, 12.9 Hz, 2H), 3.31 (s, 3H), 3.14 (quin, *J* = 5.7 Hz, 1H), 2.81 (t, *J* = 7.0 Hz, 2H), 2.38 -2.28 (m, 2H), 2.25 - 2.15 (m, 4H), 1.46 - 1.39 (m, 2H), 1.32 - 1.21 (m, 10H), 0.88 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.4, 138.9, 130.8, 128.7, 128.6, 127.5, 126.4, 80.6, 56.4, 40.5, 36.5, 36.2, 35.7, 33.3, 31.8, 29.7, 29.6, 28.6, 25.3, 22.6, 14.0; IR (KBr): υ 3026, 2961, 2931, 2865, 1636, 1534, 1452, 1364, 1218, 1031, 887, 747 cm^{-1}; HRMS (ESI) *m/z* calcd for $C_{23}H_{37}O_2NNa$ $[M+Na]^+$ 382.2719, found: 382.2716; $[\alpha]_D^{20}$ -9.1 (*c* 0.43, $CHCl_3$). Lit.[1] $[\alpha]_D^{26}$ -9.3 (*c*, 0.45, $CHCl_3$).