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Total synthesis of hirsutellide A

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Abstract—The total synthesis of hirsutellide A **1** was described. The linear hexadepsipeptide precursor **2** was synthesized in 45% yield from *N*-Boc-Me-Gly by three coupling reactions with DCC, HATU and BOP–Cl, respectively. Macrocyclization was successfully performed on the fully deprotected amino acid **14** with BOP–Cl in 15% yield and with FDDP in 22% yield.
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Hirsutellide A **1**, an 18-membered cyclic depsipeptide isolated from the cell extracts of *Hirsutella kobayasii* BCC 1660, exhibits antimycobacterial activity with a MIC (minimum inhibitory concentration) of 6–12 μg/mL with no cytotoxic effect towards Vero cells at 50 μg/mL and weak in vitro antimalarial activity with an IC_{50} value of 2.8 μg/mL.[1] The retrosynthetic analysis of hirsutellide A **1** is shown in Figure 1.

Ring closure can be achieved by either amide bond or ester bond formation. In this letter, the macrocyclization of linear precursor **2** through the formation of the amide bond from the amino function of the isoleucine residue and the carboxylic acid function of the 2-hydroxy-3-phenylpropanoic acid residue was chosen. Firstly, the formation of an amide bond is more rapidly and the formation does not require a high level of activation of the

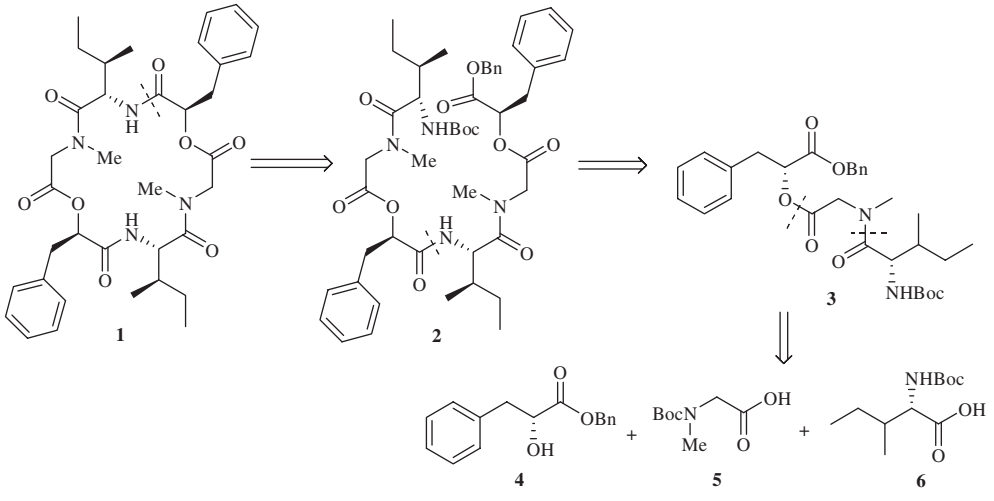

Figure 1. Retrosynthetic analysis of hirsutellide A (**1**).

Keywords: Hirsutellide A; Cyclohexadepsipeptide; Coupled reagent; Diazotization hydrolysis; Boc protection.
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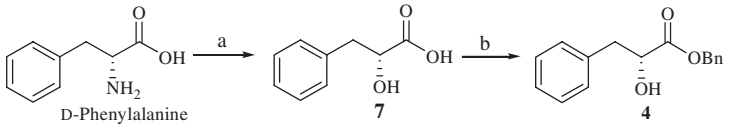
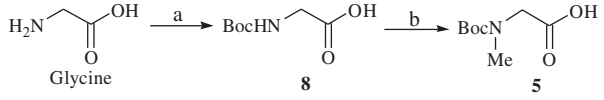


Scheme 1. Reagents and conditions: (a) $NaNO_2$, H_2SO_4, 36 h, 98%; (b) BnOH, TsOH, reflux, 4 h, toluene, 60%.

carboxyl group. Secondly, if the other amide bond was chosen, the reaction of the *N*-methyl glycine with the carboxylic acid of the isoleucine would be blocked. Now sub target molecule **2** was divided into two tridepsipeptides units **3**. Further divisions led to three subunits, 2-hydroxy-3-phenylpropanoic acid benzyl ester **4**, (*tert*-butoxycarbonyl-methyl-amino)-acetic acid **5** and 2-*tert*-butoxycarbonyl amino-3-methyl-pentanoic acid **6**.

Compound **4**[4] was obtained from D-phenylalanine through the diazotization hydrolysis[2] and esterification[3] by benzyl alcohol (Scheme 1). In the first step compound **7** was obtained as a white solid with mp 125–127 °C (lit.,[2a] 123–124 °C) and $[\alpha]_D^{20}$ +38.6 (*c* 1.00, DMF) [lit.,[2a] $[\alpha]_D^{25}$ +26.7 (*c* 3.80, acetone)].

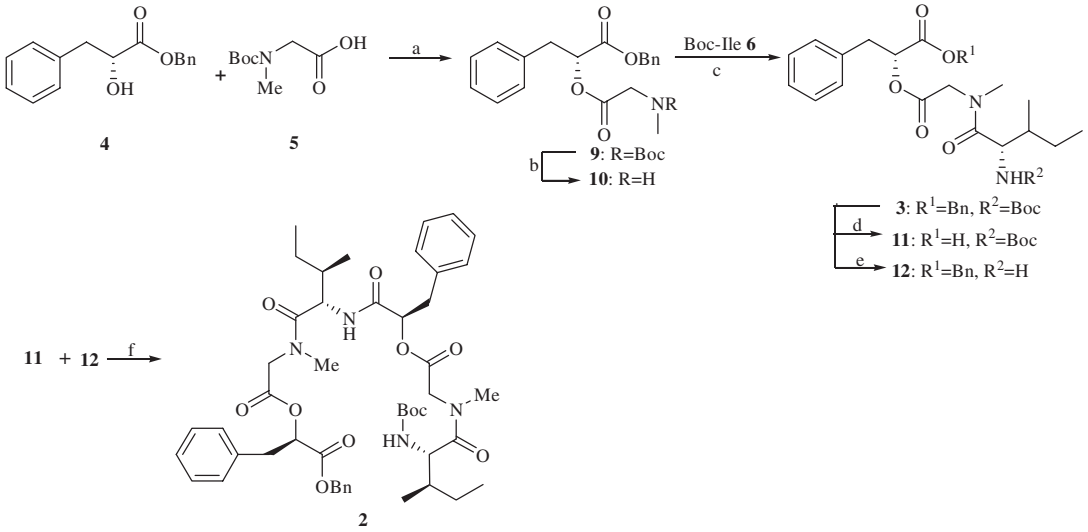
Subunit **5** was obtained from glycine by a *N*-Boc-protection and *N*-methylation with CH_3I (Scheme 2). CH_3I was added in two portions. After the addition of first part of CH_3I (4.0 equiv) and NaH (2.5 equiv), second part of CH_3I (2.0 equiv) and NaH (1.0 equiv) were added in 24 h to push the reaction to completion. Unit **6** was the *N*-Boc-protected isoleucine.



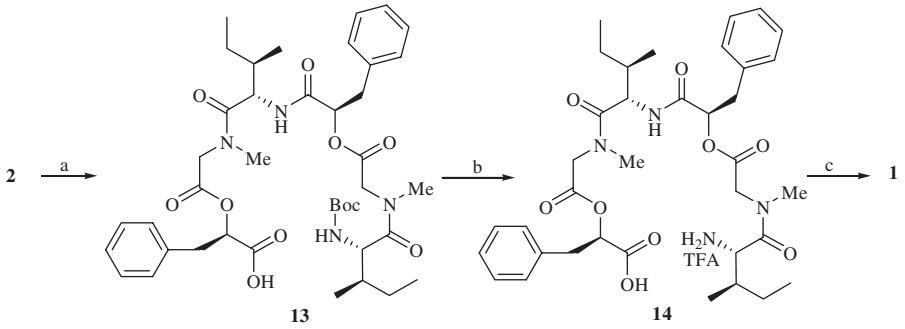
Scheme 2. Reagents and conditions: (a) Boc_2O, NaOH, THF, 0 °C to rt, 24 h; HCl, 90%; (b) CH_3I, NaH, THF, 0 °C to rt, 2 d; HCl, 92%.

The synthetic sequence of compound **2** was shown in Scheme 3. Esterification of **4** (1.0 equiv) and **5** (1.0 equiv) using DCC (1.1 equiv) and HOBt (1.1 equiv) as catalyst yielded the fully protected didepsipeptide **9**.[5] Removal of the Boc protecting group by treatment with TFA (6.5 equiv) afforded compound **10**. Then the amine TFA salt **10** (1.0 equiv) was coupled with unit **6** (1.1 equiv) by using triethylamine (10.0 equiv) as base, DMAP (0.1 equiv) as catalyst and three coupling reagents, respectively. The corresponding protected tridepsipeptide **3**[6] was obtained by using HATU-promoted reagent (1.2 equiv) in 81% yield, compared with PyBOP-promoted (1.2 equiv) in 60% yield and DCC (1.2 equiv) in 51.2% yield. Cleavage of the benzyl ester or the Boc group gave two deprotected precursors **11** or **12**, respectively. Subsequently the coupling reaction of the amine TFA salt **12** (1.0 equiv) and free acid residue **11** (1.0 equiv) were performed to synthesize the linear hexadepsipeptide **2** by using HATU (1.1 equiv), PyBOP (1.1 equiv) or BOP–Cl (1.1 equiv), with diisopropyl ethylamine (DIPEA) (10.0 equiv) as base and HOBt (1.1 equiv) as catalyst. Only the reaction with BOP–Cl reagent worked in 77% yield to provide the product **2**.[7]

Subsequent reductive removal of the benzyl group and cleavage of the Boc group gave the carboxylic acid amine TFA salt **14** (Scheme 4).



Scheme 3. Reagents and conditions: (a) DCC, HOBt, DCM, 0 °C to rt, 24 h, 72%; (b) TFA, DCM, 0 °C to rt, 5 h, used directly in the next step; (c) HATU, Et_3N, DMAP, DCM, 81%; (d) 5% Pd–C, H_2, AcOEt, rt, 24 h; (e) TFA, DCM, 0 °C to rt, 5 h, used directly in coupling; (f) BOP–Cl, DIPEA, HOBt, DCM, 0 °C to rt, 24 h, 77%.



Scheme 4. Reagents and conditions: (a) 5% Pd–C, H_2, AcOEt, rt, 24 h, 86%; (b) TFA, DCM, 0 °C to rt, 5 h, used directly in cyclization; (c) BOP–Cl, DIPEA, DMF, 0 °C to rt, 3 d, 15%.

The macrocyclization proceeded with BOP–Cl (4.5 equiv), DIPEA (10.0 equiv) in DMF under highly dilute conditions (1.0 L solvent/1.0 mmol reactant) in 15% yield for hirsutellide A **1**. And the yield was 22% when the coupling reagent FDDP (4.5 equiv) was used instead of BOP–Cl. The structure was determined by mass spectrometry and NMR spectroscopy.[8] The rotation value is consistent with the value of natural product.[1]

In conclusion, the antimycobacterial cyclohexadepsipeptide hirsutellide A **1** has been prepared in nine steps starting from 2- hydroxy-3-phenylpropanoic acid benzyl ester **4**, (*tert*-butoxycarbonyl-methyl-amino)-acetic acid **5** and 2-*tert*-butoxycarbonyl amino-3-methyl-pentanoic acid **6**. The linear hexadepsipeptide precursor **2** was synthesized in 45% yield based on compound **5** using three coupling reactions with DCC, HATU and BOP–Cl, respectively. The macrocyclization was successfully performed on the fully deprotected amino acid **14** with BOP–Cl in 15% yield and with FDDP in 22% yield.

References and notes

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3. Furuta, K.; Gao, Q.; Yamamoto, H. *Org. Synth., Coll. Vol. 9*, 722–728.
4. Analytical data of compound **4**: $[\alpha]_D^{20}$ +54.9 (*c* 1.5, DCM) [lit.,[2a] $[\alpha]_D^{25}$ +55.2 (*c* 1.88, DCM)]; IR (KBr) ν_{max}: 3484, 3034, 2928, 1737, 1495, 1450, 1380, 1264, 1189, 1094, 745, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.18–7.41 (m, 10H), 5.20 (s, 2H), 4.51 (dd, 1H, J_1 = 4.8 Hz, J_2 = 6.4 Hz), 3.15 (dd, 1H, J_1 = 4.8 Hz, J_2 = 13.6 Hz), 3.01 (dd, 1H, J_1 = 6.4 Hz, J_2 = 13.6 Hz), 2.92 (br, OH); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 173.85, 136.09, 134.94, 129.40, 128.50, 128.44, 128.23, 126.67, 71.17, 67.18, 40.34.
5. Analytical data of compound **9**: $[\alpha]_D^{20}$ +16.3 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 2970, 2932, 1754, 1703, 1453, 1381, 1243, 1179, 1160, 1070, 746, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (rotamer): 7.14–7.32 (m, 10H), 5.30–5.32 (m, 1H), 5.08–5.15 (m, 2H), 3.91–4.05 (m, 2H), 3.10–3.18 (m, 2H), 2.79, 2.78 (s, 3H, rotamer), 1.26–1.46 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamer): 169.05, 168.64, 155.60, 154.95, 135.20, 135.13, 134.84, 129.16, 129.06, 128.31, 128.28, 128.26, 128.19, 128.09, 128.05, 126.81, 79.83, 79.77, 73.09, 73.01, 66.86, 50.39, 49.68, 36.98, 34.93, 28.06, 27.87.
6. Analytical data of compound **3:** $[\alpha]_D^{20}$ +6.3 (*c* 1.0, $CHCl_3$); IR (KBr) ν_{max}: 3409, 3316, 2969, 1753, 1708, 1652, 1497, 1402, 1377, 1246, 1176, 1075, 1031, 745, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ (rotamer): 7.10–7.34 (m, 10H), 5.31 (dd, 1H, J_1 = 5.2 Hz, J_2 = 7.6 Hz), 5.04–5.17 (m, 3H), 4.51 (br, NH), 4.53 (d, 1H, J = 17.6 Hz), 3.80 (d, 1H, J = 17.6 Hz), 3.16 (dd, 1H, J_1 = 5.2 Hz, J_2 = 14.4 Hz), 3.10 (dd, 1H, J_1 = 7.6 Hz, J_2 = 14.4 Hz), 3.00 (s, 3H), 1.66–1.71 (m, 1H), 1.40 (s, 9H), 0.88–0.96 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (rotamer): 173.12, 168.95, 168.38, 155.83, 135.23, 134.97, 129.33, 128.56, 128.52, 128.49, 128.42, 128.36, 127.13, 79.48, 73.43, 67.23, 54.22, 49.16, 38.03, 37.15, 36.36, 28.32, 23.91, 15.55, 11.29.
7. Analytical data of compound **2**: $[\alpha]_D^{20}$ +1.06 (*c* 3.16, $CHCl_3$); IR (KBr) ν_{max}: 3309, 2963, 2931, 1753, 1705, 1645, 1501, 1465, 1406, 1376, 1250, 1176, 1071, 745, 707 cm^{-1}; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.24, 172.53, 168.84, 168.67, 168.19, 167.47, 156.06, 136.29, 135.28, 134.90, 130.83, 129.32, 129.29, 129.25, 128.56, 128.53, 128.48, 128.45, 128.40, 128.39, 128.35, 128.28, 127.07, 126.90, 126.79, 79.19, 74.79, 73.42, 67.21, 65.47, 54.00, 52.38, 49.06, 38.00, 37.27, 36.83, 36.28, 30.51, 29.61, 28.40–28.38 (3C), 24.27, 24.24, 15.37, 15.20, 10.84, 10.57. MS: m/z = 895.5 $(M+Na)^+$.
8. Analytical data of compound **1**: $[\alpha]_D^{20}$ −13.8 (*c* 0.22, $CHCl_3$) [lit.,[1] $[\alpha]_D^{28}$ −13.6 (*c* 0.25, $CHCl_3$)]; IR (film) ν_{max}: 3283.69, 3018.56, 2962.65, 2927.93, 1753.57, 1661.38, 1630.27, 1529.52, 1482.58, 1060.54 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 7.54 (d, 2NH, J = 10.0 Hz), 7.29–7.14 (m, 10H), 5.61 (dd, 2H, J_1 = 2.8 Hz, J_2 = 11.6 Hz), 4.91 (t, 2H, J = 10.2 Hz), 4.44 (d, 2H, J = 17.2 Hz), 3.66 (dd, 2H, J_1 = 2.8 Hz, J_2 = 14.0 Hz), 3.25 (s, 6H), 3.17 (d, 2H, J = 17.2 Hz), 2.73 (dd, 2H, J_1 = 11.6 Hz, J_2 = 14.0 Hz), 2.27–2.20 (m, 2H), 1.57–1.51 (m, 2H), 1.27–1.14 (m, 2H), 0.90 (t, 6H, J = 7.4 Hz), 0.85 (d, 6H, J = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 174.08, 168.77, 166.82, 136.16, 129.11, 128.58, 127.11, 74.07, 52.33, 51.75, 38.73, 37.90, 35.86, 24.27, 15.38, 10.17. HR-MS (FAB) m/z calcd for $C_{36}H_{49}N_4O_8$ (M+1) 665.3550, found 665.3545.