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Scientific paper

Stereoselective Synthesis of Southern Fragment of Hantupeptin A

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Abstract

The stereoselective synthesis of the southern fragment (C21–C41) of Hantupeptin A is described. The required stereochemistry of β-hydroxy-α-methyl acid unit was accomplished through the Aldol reaction using Evan's chiral auxiliary followed by the installation of the terminal alkyne with Ohira–Bestmann reagent.

Keywords: Hantupeptin A, Aldol Reaction, Stereoselective synthesis, Peptide; Evan's auxiliary

1. Introduction

Novel bioactive metabolites are emerging as an important source of pharmacologically active compounds or promising lead structures in drug discovery.[1–5] Naturally occurring cyclic peptides[6] have come within this class possessing diverse biological activities like immunosuppressant, antibiotic, antifungal, anti-inflammatory and anticancer effects.[7] Indeed, marine organisms such as algae, sponges, and coelenterates became an exceptional source of these natural products. Since the discovery of the didemnins, this class of natural products continues to stimulate active research in synthetic and medicinal chemistry, as well as in clinical oncology and cell biology.[8] In 2009, Tan and co-workers have isolated a new cyclodepsipeptide, hantupeptin A (**1**) from the marine cyanobacterium *Lyngbya majuscula*. The hantupeptin A (**1**) has exhibited cytotoxicity against MOLT-4 leukemia cells and MCF-7 breast cancer cells with IC_{50} values of 32 and 4.0 μM, respectively.[9] The extensive spectral studies and advanced chiral techniques have revealed the planar structure as well as the absolute configuration of **1**. Structurally, compound **1** is a 19-membered cyclic tetrapeptide, which consists of ?ve α-amino/hydroxy acid residues, including phenyl lactic acid, proline, *N*-methylvaline, valine, *N*-methylisoleucine and a α-methyl-β-hydroxy acid unit with an alkyne at the terminal end of the molecule. The stereochemistry at the hydroxyl group attached carbon (C-35) of an unusual hydroxy acid, 3-hydroxy-2-methyloctynoic acid (Hmoya) unit **4** was determined as *S* using the Mosher's analysis. However, the stereochemistry at the methyl group attached carbon (C-34) was not reported at that point of time.

Later, in 2010, the same group has isolated hantupeptins B (**2**) and C (**3**) along with **1** from the organic extracts of the same marine cyanobacterium.[10] The only structural difference among these molecules is the degree of unsaturation in the unusual amino acid part, where **1** is having a terminal alkyne functionality, **2** has an alkene and **3** is without any unsaturation in its structure (Figure 1). Compounds **2** and **3** also showed moderate *in vitro* cytotoxicity against MOLT-4 (leukemic) and MCF-7 (breast cancer) cell lines. In the study of the re-isolation of compound **1**, the relative stereo chemistry at C-34 carbon of Hmoya unit was determined as *R* by the rigorous NMR experiments. Very recently, the absolute configuration of

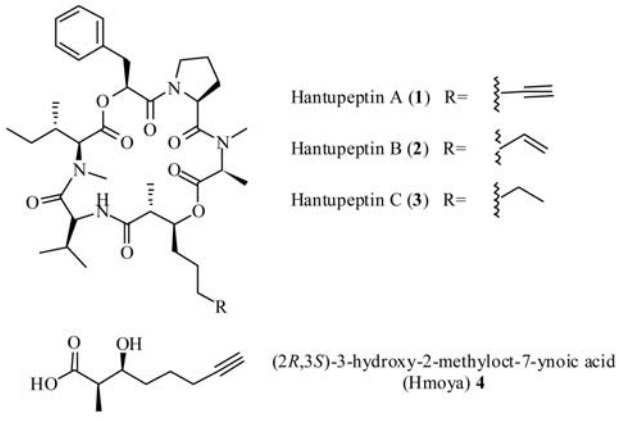


Figure 1: Structures of Hantupeptins A–C.

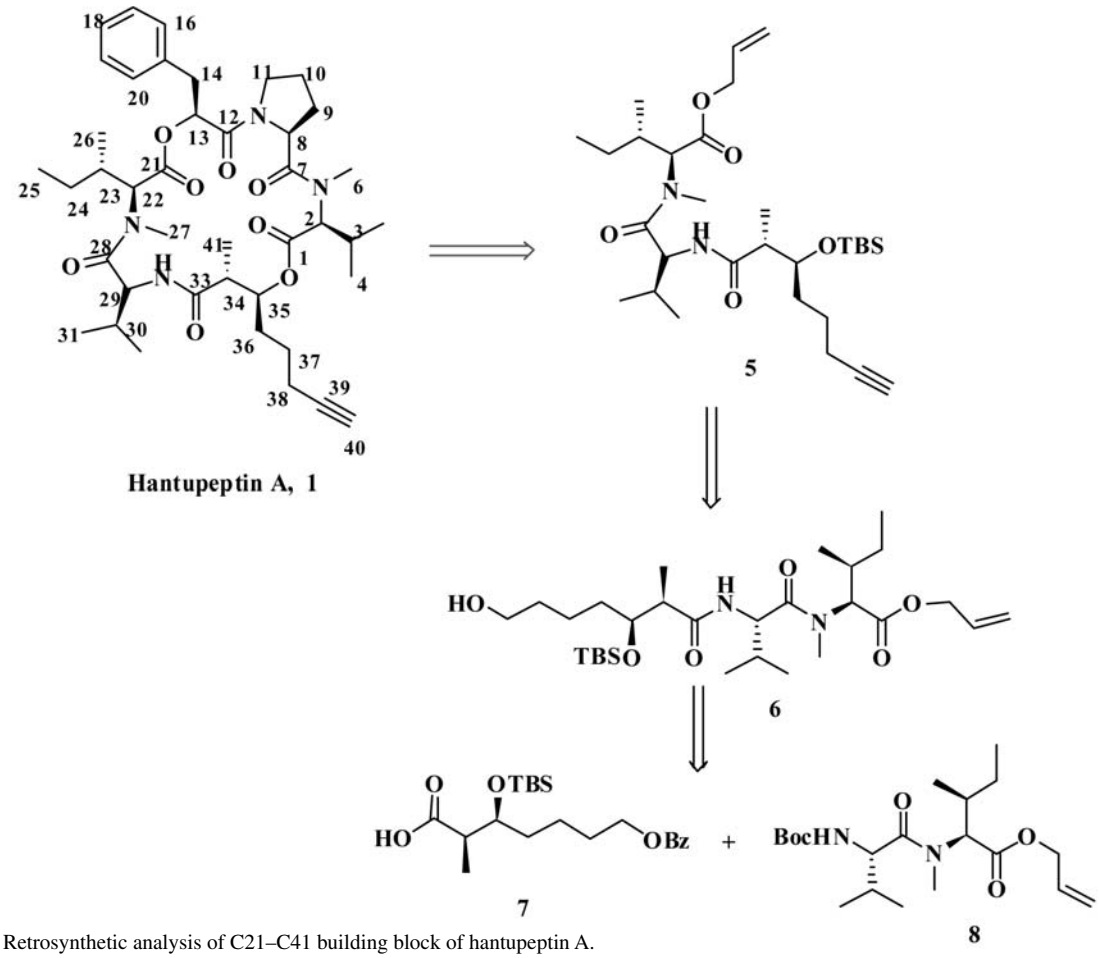
Hmoya unit of hantupeptin C (**3**) was assigned as (2*R*,3*S*) based on the retention times of the Mosher ester derivative standards by RPLC-MS.[11] Till date, no synthetic efforts have been reported in the literature for these molecules. In continuation of our interest on the synthesis of biologically active molecules,[12] we have reported the synthesis of hantupeptin A C21–C41 fragment with the unusual component, Hmoya residue as a part of it. The Hmoya unit **4** is also present in a number of marine-derived compounds, such as onchidin B, kulomo'opunalide-1, kulomo'opunalide-2, and trungapeptin A.

2. Results and Discussion

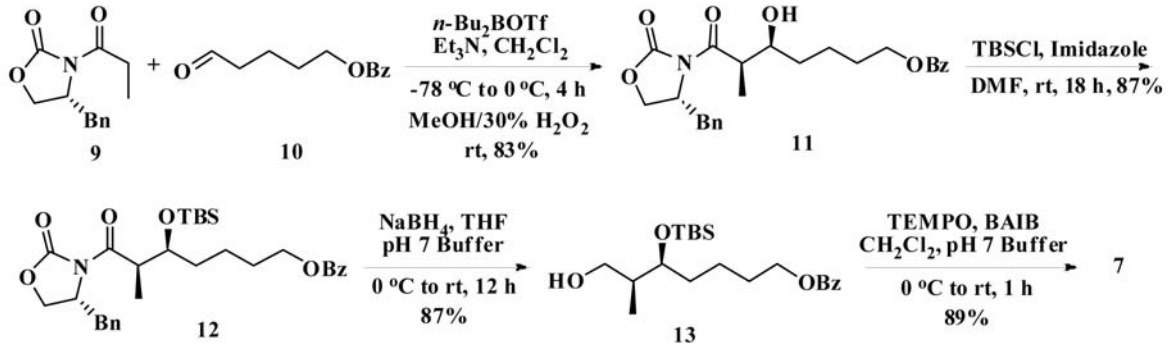
From the retrosynthetic outlook (Scheme 1), the desired molecule was envisioned to be obtained from the key intermediate **5**, which, in turn may be built from **6** through oxidation followed by Ohira–Bestmann reaction. Compound **6** could be obtained by coupling compound **7** with an amine, derived from compound **8**. The stereocentres in compound **7** could be achieved through Evan's *syn* aldol protocol followed by a reductive etherification. The stereochemistry in compound **8** was achieved from the natural amino acids *L*-isoleucine and *L*-valine.

Preparation of the acid 7. The synthesis began with Evan's aldol reaction between the aldehyde **10** and oxazolidinone **9**. Aldehyde **10** was prepared in two steps from the inexpensive 1,5-pentanediol following the reported procedure.[13] The other, desired (*R*)-4-benzyl-3-propionyloxazolidin-2-one **9** was also smoothly obtained using well documented literature protocol.[14] The di-*n*-butylboron triflate mediated Aldol reaction between compounds **9** and **10** furnished the *syn*-product **11** in 83% yield (Scheme 2). Protection of the secondary hydroxy group of the compound **11** as TBS-ether **12** was achieved in 87% yield by exposing to TBSCl/Imidazole in CH_2Cl_2 at room temperature for 18 h. Compound **12** was then treated with sodium borohydride in THF/pH 7 buffer at room temperature for the reductive removal of the auxiliary to provide alcohol **13**. The primary hydroxyl group of compound **13** was oxidized to a carboxylic acid using (bisacetoxyiodo)benzene (BAIB) / 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) in CH_2Cl_2/pH 7 buffer to obtain the acid fragment **7** in 89% yield.

Preparation of compound 8. The synthesis of compound **8** was commenced by carrying out the preparation of the known *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*-isoleucine **14** from *L*-isoleucine using the literature procedure.[15] Esterification of the acid **14** with allyl bromide was clean-



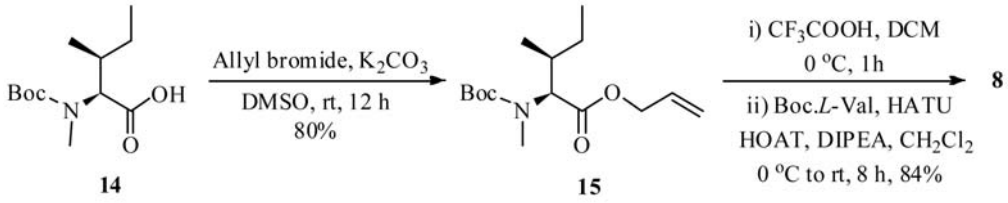
Scheme 1: Retrosynthetic analysis of C21–C41 building block of hantupeptin A.



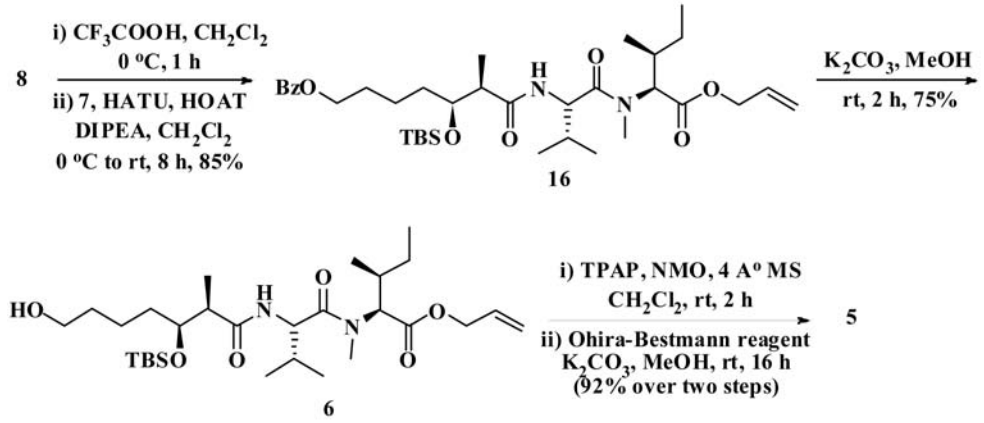
Scheme 2: Synthesis of the acid fragment **7**.

ly achieved by using K_2CO_3 in DMSO solvent at room temperature, to get the ester **15** in 80% yield. The required amide **8** was prepared from **15** by two transformations. First treating with TFA in CH_2Cl_2 to get secondary amine in good yields and used as such for the next step without further purification. Later, the crude amine, prepared from **15** was coupled with (*tert*-butoxycarbonyl)-*L*-valine under standard reaction conditions in the presence of 1-hydroxy-7-azabenzotriazole (HOAt) and 1-[bis(dimethylamino) methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium-3-oxide hexafluorophosphate (HATU) as coupling agents and *N*,*N*-diisopropyl ethylamine (DIPEA) as the base in anhydrous CH_2Cl_2 as the solvent at room temperature for 8 h to acquire the desired dipeptide fragment **8** in 84% yield (Scheme 3).

Construction of C21–C41 segment from 7 and 8. With the successful completion of the desired fragments **7** and **8**, the attention was turned to couple them to give the di-amide **16**. For that, intially the boc protection of compound **8** was removed by using TFA in CH_2Cl_2 at 0 °C and then coupled with the compound **7** under HATU/HOAt conditions at room temperature, to obtain the required product **16** in 85% yield. The resulting compound **16** was hydrolyzed with potassium carbonate in methanol to give the primary alcohol **6** in 75% yield which upon the oxidation with TPAP/NMO to the aldehyde followed by the treatment with Ohira–Bestmann reagent gave the targeted terminal alkyne product **5** in 92% yield (Scheme 4).



Scheme 3: Synthesis of the fragment **8**.



Scheme 4: Construction of the C21-C41 building block.

3. Experimental

NMR spectra were recorded in $CDCl_3$ on Bruker AM-300 (300 MHz) spectrometer at ambient temperature. Chemical shifts are reported in ppm relative to TMS as internal standard and coupling constants are reported in Hz. FTIR spectra were recorded on a Nicolet FT-IR 400 spectrometer in KBr or as neat. Optical rotations were measured on an Perkin–Elmer 141 polarimeter by using a 2 mL cell with a path length of 1 dm with $CHCl_3$ or $CDCl_3$ as solvent. Low resolution mass spectra were obtained on VG 70–70H or LC/MSD trap SL spectrometer operating at 70 eV using direct inlet system. High resolution mass spectra (HRMS) were recorded on an Agilent Technologies 6510 Q-TOF spectrometer. Technical-grade EtOAc and hexanes used for column chromatography were distilled before use. All the reagents and solvents were of reagent grade and used without further purification unless otherwise stated.

(5*S*,6*R*)-7-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-6-methyl-7-oxoheptyl benzoate (11): To a stirred solution of acyl oxazolidinone **9**[14] (1.04 g, 4.45 mmol) in CH_2Cl_2 (10 mL) was added dropwise *n*-Bu_2BOTf (1.0 M in CH_2Cl_2, 4.67 mL, 4.67 mmol) and stirred for 10 min. *i*-Pr_2NEt (0.93 mL, 5.34 mmol) was then added dropwise and the reaction was stirred at the same temperature for 1 h. The mixture was cooled to –78 °C before a solution of aldehyde **10**[12] (1.02 g, 4.95 mmol) in CH_2Cl_2 (15 mL) was added dropwise via cannula. Stirring was continued at –78 °C for 3 h before gradually warming to 0 °C. The reaction mixture was stirred for additional 3 h at 0 °C and then quenched by the addition of 0.1 M pH 7 phosphate buffer (7.5 mL) followed by MeOH (10 mL) at 0 °C. After stirring for 5 min, a solution of 30% aqueous H_2O_2 (7.5 mL) in MeOH (15 mL) was added dropwise and stirred at the same temperature for 1 h before being concentrated under reduced pressure. The residue was diluted with Et_2O, the phases were separated and the aqueous phase extracted with Et_2O. The combined organic phase was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography over silica gel (35% ethyl acetate in pet. ether) gave **11** (1.63 g, 83%) as a viscous, colorless oil. IR ($CHCl_3$): ν 3250, 2936, 1780, 1710, 1453, 1386, 1277, 1214, 1146, 763, 506 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–7.98 (m, 2H), 7.55 (t, J = 7.42 Hz, 1H), 7.43 (t, J = 7.5 Hz), 7.39–7.24 (m, 3H), 7.20 (d, J = 5.6 Hz, 2H), 4.71 (ddt, J = 10.4, 6.9, 3.3 Hz, 1H), 4.33 (t, J =6.5 Hz, 2H), 4.28–4.13 (m, 2H), 4.04–3.93 (m, 1H), 3.77 (qd, J = 7.0, 2.7 Hz, 1H), 3.25 (dd, J = 13.4, 3.2 Hz, 1H), 2.95 (s, 1H), 2.79 (dd, J = 13.4, 9.4 Hz, 1H), 1.87–1.42 (m, 6H), 1.27 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 178.0, 166.8, 153.3, 135.2, 133.1, 130.0, 129.0, 128.0, 127.3, 71.6, 66.2, 65.1, 55.1, 42.2, 38.2, 33.0, 28.5, 23.0, 10.4; HRMS (ESI): *m*/*z* calculated for $C_{25}H_{30}O_6N$: $[M+H]^+$ 440.2067, found 440.2044; $[\alpha]_D^{25}$ = +29.0 (*c* 1.62, $CDCl_3$).

(5*S*,6*R*)-7-((*R*)-4-Benzyl-2-oxooxazolidin-3-yl)-5-(*tert*-butyldimethylsilyloxy)-6-methyl-7-oxoheptyl benzoate (12): To a stirred solution of **11** (1.60 g, 3.64 mmol) in DMF (15 mL) were added imidazole (800 mg, 12.3 mmol) and TBSCl (*tert*-butylchlorodimethylsilane) (950 mg, 7.4 mmol). After 18 h at 25 °C, the reaction mixture was added to 20% CH_2Cl_2: hexane (100 mL) and successively washed with 10% aq. $NaHSO_3$ (25 mL) and water (2 × 25 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo and distilled to yield **12** (1.74 g, 87%) as a colorless oil. IR ($CHCl_3$): ν 3349, 3380, 3088, 2971, 2934, 1699, 1740, 1472, 1452, 1391, 1368, 1311, 1256, 1152, 992, 933, 771, 666, 560 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–7.98 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 2H), 7.28–7.38 (m, 3H), 7.20 (d, J = 7.0 Hz, 2H), 4.6 (ddt, J = 10.2, 6.4, 3.1 Hz, 1H), 4.33 (t, J = 6.5 Hz, 2H), 4.12–4.27 (m, 2H), 4.02 (q, J = 5.4, 5.6 Hz, 1H), 3.88 (qd, J = 6.8, 1.6 Hz, 1H), 3.30 (dd, J = 13.2, 3.0 Hz, 1H), 2.78 (dd, J = 13.2, 9.6 Hz, 1H), 1.70 (m, 2H), 1.62–1.42 (m, 4H), 1.22 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.2, 166.3, 153.0, 135.0, 133.1, 129.3, 129.1, 128.1, 127.6, 72.6, 65.7, 64.7, 56.3, 43.2, 35.0, 29.2, 26.3, 22.0, 19.0, 12.3, –4.5; HRMS (ESI): *m*/*z* calculated for $C_{31}H_{47}O_6N_2Si$: $[M+Na]^+$ 571.3197, found 571.3174; $[\alpha]_D^{25}$ = +10.53 (*c* 1.33, $CDCl_3$).

(5*S*,6*S*)-5-(*tert*-Butyldimethylsilyloxy)-7-hydroxy-6-methylheptyl benzoate (13): To a stirred solution of **12** (1.70 g, 3.07 mmol) in THF (70 mL) at 0 °C was added a solution of $NaBH_4$ (579 mg, 15.3 mmol) in pH 7 buffer (18.5 mL). The resulting solution was stirred for 10 min at 0 °C before being allowed to gradually warm to room temperature and continued stirring for overnight. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and stirred at room temperature for 1 h. The separated aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. Flash chromatography over silica gel (15% ethyl acetate in pet. ether) gave **13** (1.01 g, 87%) as a colorless oil. IR ($CHCl_3$): ν 3436, 2954, 2930, 2857, 1721, 1459, 1275, 1113, 1033, 836, 773, 712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–8.10 (m, 2H), 7.55 (t, J = 7.3 Hz, 1H), 7.43 (t, J = 7.9 Hz, 2H), 4.70 (s, 1H), 4.33 (t, J = 6.7 Hz, 2H), 3.79–3.75 (m, 1H), 3.70 (t, J = 9.0 Hz, 2H), 3.56–3.48 (m, 1H), 1.97 (m, 1H), 1.56–1.32 (m, 6H), 0.90 (s, 9H), 0.82 (d, J = 7.8 Hz, 3H), 0.20 (s ,6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 166.7, 132.8, 130.1, 129.3, 128.4, 77.4, 65.5, 64.8, 39.4, 32.0, 28.7, 25.9, 22.7, 17.9, 12.1, –4.6; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{37}O_4Si$: $[M+H]^+$ 381.24556, found 381.24414.

(2*R*,3*S*)-7-(Benzoyloxy)-3-(*tert*-butyldimethylsilyloxy)-2-methylheptanoic acid (7): To a stirred solution of **13** (1.0 g, 2.62 mmol) in CH_2Cl_2 (5 mL) at 0 °C were added

BAIB (3 g, 9.31 mmol), catalytic amount of TEMPO in p-H 7 buffer (3 mL). The resulting solution was stirred for 10 min at 0 °C before being allowed to gradually warm to room temperature with stirring for 1 h. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and stirred at room temperature for 1 h. The separated aqueous phase was extracted with EtOAc (2 × 25 mL). The combined organic phase was washed with brine, dried over anhydrous Na_2SO_4 filtered and concentrated under reduced pressure. Flash chromatography over silica gel (30% ethyl acetate in pet. ether) gave **7** (0.92 g, 89%) as a colorless oil. IR ($CHCl_3$): ν 2931, 2857, 1715, 1459, 1386, 1274, 1220, 1110, 1069, 1026, 936, 836, 773, 711, 675 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.10–7.98 (m, 2H), 7.50 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 4. 33 (t, J = 6.7 Hz, 2H), 3.99 (q, J = 6.0, 5.2 Hz, 1H), 2.66–2.56 (m, 1H), 1.72–1.30 (m, 6H), 1.22 (d, J = 6.8 Hz, 3H), 0.90 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.6, 134.2, 130.0, 129.9, 128.4, 73.5, 65.3, 44.5, 33.5, 29.2, 26.2, 22.2, 18.4, 11.5, –5.4; HRMS (ESI): *m*/*z* calculated for $C_{21}H_{34}O_5Si$: $[M+H]^+$ 393.4556, found 392.4414.

(2*S*,3*S*)-Allyl-2-(*tert*-butoxycarbonyl(methyl)amino)-3-methylpentanoate (15): Na_2CO_3 (2.55 g, 24.3 mmol) and Boc_2O (3.94 g, 18.2 mmol) were added to a solution of *L*-isoleucine (3.5 g, 12.3 mmol), in H_2O (20 mL) and THF (5 mL) at 0 °C. After the reaction mixture has been stirred at room temperature for 12 h, it was neutralized with HCl (10%) until pH 2 has been reached. The mixture was then extracted with EtOAc (3 × 50 mL), washed with brine, dried over Na_2SO_4. Concentration gave the crude *N*-Boc-isoleucine (2.6 g, 100%). NaH (60% in mineral oil, 2.45 g, 61.3 mmol) was added in portions to a solution of *N*-Boc-isoleucine (2.6 g, 9.09 mmol) and MeI (6.05 mL) in THF (50 mL) at 0 °C. After the reaction mixture has been stirred at room temperature for 36 h, it was poured into saturated NH_4Cl solution (250 mL), extracted with EtOAc (3 × 150 mL) and dried over Na_2SO_4. Concentration gave *N*-methyl-*N*-Boc-isoleucine (2.53 g, 92%). K_2CO_3 (3.08 g, 22.3 mmol) and allyl bromide (1.4 mL, 16.9 mmol) were added to a solution of *N*-methyl-*N*-Boc-isoleucine (2.53 g, 10.9 mmol) in DMSO (40 mL). After the mixture has been stirred at room temperature for 12 h, it was portioned between EtOAc (75 mL) and brine (75 mL). The organic phase was separated and aqueous phase was extracted with EtOAc (2 × 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography gave **15** (2.5 g, 80.9%). IR ($CHCl_3$): ν 3089, 2971, 2936, 2880, 1741, 1701, 1650, 1480, 1456, 1393, 1367, 1313, 1255, 1183, 1145, 1047, 990, 931, 871, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.97–5.84 (m, 1H), 5.34–5.20 (m, 1H), 4.62–4.60 (m, 2H), 4.55 (d, J = 11.1 Hz, 1H), 4.26* (d, J = 11.1 Hz, 1H), 2.81 (s, 3H), 2.78* (s, 3H), 2.04–1.95 (m, 1H), 1.45 (m, 10H), 1.13–1.01 (m, 1H), 0.92 (d, J = 6.0 Hz, 3H), 0.87 (d, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 156.4, 132.1, 118.4, 80.3, 65.6, 63.8, 33.5, 30.8, 28.7, 24.5, 15.6, 10.4; HRMS (ESI): *m*/*z* calculated for $C_{15}H_{28}O_4N$: $[M+H]^+$ 286.20128, found 286.19969. $[\alpha]_D^{25}$ = -74.7 (*c* 1.1, $CHCl_3$). *denotes the rotamer peaks.

(2*S*,3*S*)-Allyl-2-((*S*)-2-(*tert*-butoxycarbonylamino)-*N*,3-dimethylbutanamido)-3-methylpentanoate (8): A solution of (*tert*-butoxycarbonyl)-*L*-valine (0.35 g, 1.22 mmol), HATU (0.24 g, 1.8 mmol) and HOAt (0.34 g, 1.8 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C under N_2 atmosphere for 15 min, treated sequentially with salt [prepared from **15** (375 mg, 1.24 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C on treatment with CF_3COOH (0.1 mL)] and DIPEA (0.6 mL, 3.6 mmol) and stirred for 8 h. The reaction mixture was quenched with aq. satd. NH_4Cl solution (10 mL). After 10 min, it was diluted with $CHCl_3$ (2 × 10 mL) and washed with water (10 mL), $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, evaporated and the residue was purified by column chromatography (60–120 mesh silica gel, 35% ethyl acetate in pet. ether) to afford **8** (509 mg, 84%) as a colorless syrup. IR ($CHCl_3$): ν 3333, 2966, 2945, 2862, 1742, 1706, 1658, 1462, 1367, 1294, 1178, 1001, 938, 876, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.40–5.41 (m, 1H), 5.05 (d, J = 2.2 Hz, 2H), 4.40 (q, J = 2.6 Hz, 1H), 3.70 (s, 3H), 3.70–3.50 (m, 1H), 3.50–3.10 (m, 2H), 3.09 (s, 2H), 2.10–1.89 (m, 2H), 1.50 (s, 9H), 1.32–1.10 (m, 5H), 1.00–0.80 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.4, 156.4, 118.6, 79.8, 60.4, 55.3, 52.2, 33.4, 31.4, 29.8, 24.5, 19.8, 16.4, 11.2; HRMS (ESI): *m*/*z* calculated for $C_{20}H_{36}N_2O_5Na$: $[M+Na]^+$ 407.2562, found 407.2414.

(5*S*,6*R*,9*R*,12*S*)-Allyl-5-(4-(benzoyloxy)butyl)-12-*sec*-butyl-9-isopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (16): A solution of acid **7** (510 mg, 1.29 mmol), HATU (240 mg, 1.8 mmol) and HOAt (340 mg, 1.8 mmol) in CH_2Cl_2 (5 mL) was stirred at 0 °C under N_2 atmosphere for 15 min, treated sequentially with TFA salt [prepared from **8** (450 mg, 1.2 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C on treatment with CF_3COOH (0.1 mL)] and DIPEA (0.6 mL, 3.6 mmol) and stirred for 8 h. The reaction mixture was quenched with aq. satd. NH_4Cl solution (10 mL). After 10 min, it was diluted with $CHCl_3$ (2 × 10 mL) and washed with water (10 mL), $NaHCO_3$ solution (10 mL) and brine (10 mL). The organic layers were dried over Na_2SO_4, evaporated and the residue purified by column chromatography (60–120 mesh silica gel, 45% ethyl acetate in pet. ether) to afford **16** (725 mg, 85%) as a colorless syrup. IR ($CHCl_3$): ν 3347, 3233, 2966, 2926, 2915, 2854, 2840, 1739, 1701, 1667, 1651, 1460, 1448, 1380, 1220, 1172, 1110, 1069, 1026, 1003, 936, 836, 773, 771, 711, 676, 667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.00 (d, J = 7.5 Hz, 2H), 7.55 (d, J = 8.3 Hz, 1H), 7.43 (t, J = 7.5 Hz, 2H), 5.96–5.79 (m, 1H), 5.39–5.18 (m, 2H), 5.11–5.01 (m, 1H),

4.65–4.54 (m, 2H), 4.34–7.27 (m, 3H), 3.82–3.68 (m, 3H), 3.10–3.05 (m, 2H), 2.06–1.89 (m, 2H), 1.83–1.50 (m, 3H), 1.45–1.37 (m, 3H), 1.36–1.19 (m, 4H), 1.20–1.05 (m, 1H), 1.01–0.78 (m, 22H), 0.10–0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 171.2, 168.4, 133.5, 132.5, 130.5, 129.2, 74.5, 66.0, 65.3, 60.1, 58.2, 54.1, 49.2, 34.2, 32.1, 30.1, 29.4, 26.2, 25.1, 19.2, 16.4, 14.4, 11.2, –5.4. HRMS (ESI): *m*/*z* calculated for $C_{36}H_{60}N_2O_7SiNa$: $[M+Na]^+$ 683.4556, found 683.4214.

(5*S*,6*R*,9*S*,12*S*)-Allyl-12-((*S*)-*sec*-butyl)-5-(4-hydroxybutyl)-9-isopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (6): To a stirred solution of **16** (700 mg, 1.06 mmol) in MeOH (5 mL) was added K_2CO_3 (45 mg, 0.33 mmol). The reaction was stirred at room temperature until complete by TLC (2 h). The mixture was then diluted with CH_2Cl_2 (25 mL) and washed with H_2O (5mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase dried over Na_2SO_4, filtered, evaporated and the residue was purified by column chromatography (60–120 mesh silica gel, 52% ethyl acetate in pet. ether) to afford **6** (440 mg, 75%) as a colorless syrup. IR ($CHCl_3$): ν 3347, 3300, 3233, 2956, 2926, 2925, 2854, 2840, 1701, 1667, 1651, 1460, 1448, 1380, 1220, 1172, 1110, 1069, 1026, 1003, 936, 836, 773, 771, 711, 676, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.96–5.79 (m, 1H), 5.39–5.18 (m, 2H), 5.11–5.01 (m, 1H), 4.65–4.54 (m, 2H), 4.50 (brs, 1H), 4.34–4.27 (m, 3H), 4.25–4.15 (m, 2H), 3.68 (m, 3H), 3.10–3.05 (m, 2H), 2.06–1.89 (m, 2H), 1.83–1.50 (m, 3H), 1.45–1.37 (m, 3H), 1.36–1.19 (m, 4H), 1.20–1.05 (m, 1H), 1.01–0.78 (m, 19H), 0.10–0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 174.1, 171.2, 132.5, 74.5, 66.0, 65.3, 62.8, 60.1, 58.2, 54.1, 49.2, 34.2, 32.1, 30.1, 29.4, 26.2, 25.1, 19.2, 16.4, 14.4, 11.2, –5.4; HRMS (ESI): *m*/*z* calculated for $C_{29}H_{56}N_2O_6SiNa$: $[M+Na]^+$ 579.3914, found 579.3812.

(5*S*,6*R*,9*S*,12*S*)-Allyl 12-((*S*)-*sec*-butyl)-9-isopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-5-(pent-4-ynyl)-4-oxa-8, 11-diaza-3-silatridecan-13-oate (5): To a stirred solution of **6** (420 mg, 0.755 mmol) and powdered 4 Å molecular sieves (650 mg) in CH_2Cl_2 (15 mL) were subsequently added 4-methylmorpholine-*N*-oxide (227 mg, 1.94 mmol) and tetrapropylammonium perruthenate (22.9 mg, 0.065 mmol) and the mixture was stirred at room temperature for 2 h. The reaction mixture was filtered through a pad of silica gel and the filtrate was concentrated under reduced pressure to give the aldehyde as a colorless oil. The residue was placed under high vaccum for 2 h before being used in the subsequent reaction without purifiation. The aldehyde, K_2CO_3 and the Ohira–Bestmen reagent (262 mg, 1.32 mmol) were stirred for 16 h. The mixture was then diluted with CH_2Cl_2 (25 mL) and washed with H_2O (5 mL). The separated aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic phase dried over Na_2SO_4, filtered and evaporated and the residue was purified by column chromatography (60–120 mesh silica gel, 5% ethyl acetate in pet. ether) to afford **5** (352 mg, 92%) as a yellow syrup. ^{1}H NMR(300 MHz, $CDCl_3$): δ 5.86–5.74 (m, 1H), 5.29–5.08 (m, 2H), 5.04–5.01 (m, 1H), 4.45–4.34 (m, 2H), 4.14–4.07 (m, 3H), 4.02–3.95 (m, 2H), 3.58 (m, 3H), 3.10–3.05 (m, 2H), 2.20 (s, 1H), 2.06–1.89 (m, 2H), 1.83–1.50 (m, 3H), 1.45–1.37 (m, 3H), 1.36–1.19 (m, 4H), 1.20–1.05 (m, 1H), 1.01–0.78 (m, 19H), 0.10–0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.1, 170.2, 129.5, 83.9, 71.5, 68.2, 61.3, 60.8, 60.1, 53.2, 52.1, 48.2, 33.2, 32.1, 30.1, 29.4, 26.2, 25.1, 18.7, 16.4, 14.4, 11.2, –5.4; HRMS (ESI): *m*/*z* calculated for $C_{30}H_{54}N_2O_5SiNa$: $[M+H]^+$ 551.3140, found 579.3120.

4. Conclusions

In conclusion, a practical and stereoselective synthesis of C21–C41 fragment of hantupeptin A having five stereo centers, two amide linkages and one ester linkage was demonstrated with differential protective groups to allow further extensions. The key features of the strategy are the successful utilization of Evan's Aldol reaction, TEMPO mediated oxidation and Ohira–Bestmann homologation. Furthur investigation towards the total synthesis of hantupeptin A are in progress.

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Povzetek

Opisana je stereoselektivna sinteza južnega fragmenta (C21–C41) hantupeptina A. Zahtevana stereokemija β-hidroksi-α-metil kislinske enote je bile dosežen z aldolno reakcijo z uporabo Evansovega kiralnega pomagala, ki ji je sledila uvedba terminalnega alkinskega ostanka s pomočjo Ohira-Bestmannovega reagenta.