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Stereoselective synthesis of C1-C24 fragment of antanapeptin-A

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Abstract: The stereoselective synthesis of the (C1-C24) fragment of Antanapeptin–A is described. The required stereochemistry of β-hydroxy-α-methyl acid unit was accomplished through Aldol reaction using Evans' chiral auxiliary followed by the installation of terminal alkyne with Ohira–Bestmann reagent.

Keywords: Antanapeptin A; Aldol Reaction; Stereo selective synthesis; Peptide; Evans' auxiliary. © 2016 ACG Publications. All rights reserved.

1. Introduction

Cyclic depsipeptides[1] have at least one ester linkage formed by replacing one or more amino acid(s) by a hydroxy acid resulting in at least one ester bond in the core ring structure. Some cyclic depsipeptides are cyclized between the *C*-terminal carboxyl and the side chain of a Thr or Ser residue in the chain. They are secondary metabolites of fungi, plants and some are originated from the marine environment. Cyclo depsipeptides show an interesting spectrum of biological activity such as immunosuppressant, antibiotic, antifungal, anti-inflammatory and anticancer effects.[2] Since the discovery of the didemnins, this class of natural products continue to stimulate active research in synthetic and medicinal chemistry, as well as in clinical oncology and cell biology.[3] Members of this new class of potential drugs may serve as lead compounds in the drug development process for pharmacologically more potent and toxicologically safe derivatives.[4-8] Some of these natural products and (semi) synthetic derivatives have already been evaluated in clinical trials. Antanapeptin A (**1**) belongs to a family of natural cyclic depsipeptides, isolated from marine sponges, marine cyanobacterium *Lyngbya majuscule* collected from Antany Mora, Madagascar along with few other natural products.[9] The structure was elucidated by interpretation of extensive 1D and 2D NMR spectroscopic data. Structurally this compound **1** is cyclic depsipeptide consisting of four α -amino acid residues, proline, *N*-methyl-Phenyl alanine, valine, *N*-methyl-isoleucine and *α,β*-hydroxy acid unit and one non-amino acid unit, 2-hydroxyisovelaric acid, with different degrees of unsaturation at the terminal end of each molecule. The absolute configurations of **1**, determined by Marfey's analysis, included L-*N*-Me-Ile, L-*N*-Me-Phe, L-Pro, and L-Val. However, the absolute configuration of 2-hydroxyisovelaric acid was not established. Further, the initial biological activity screening of antanapeptins proved that they are inactive in brine shrimp toxicity, sodium channel modulation and antimicrobial bioassays. Due to the paucity of compounds further evaluation remains uncertain. Therefore, the synthesis of antapeptins is necessary for the confirmation of structure along with absolute stereochemistry and further biological screening. Till date, there is no synthesis reported in the literature for this molecule. In continuation of our work on the synthesis of biological active molecules,[10] we have developed a strategy for the synthesis C1-C24 fragment of Antanapeptin A, which is also part of the other molecules, Antanapeptins B, C & D.[9]

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2. Results and Discussion

From the retrosynthetic outlook (Figure 1), the desired molecule was visualised to be obtained from the key intermediate **2** which in turn could be derived from **3** through oxidation followed by Ohira–Bestmann reaction. Compound **3** was envisioned to be constructed by coupling compound **4** with amine derived from compound **5**. The stereocentres in compound **4** could be obtained by utilizing lithiated aldol-reaction followed by reductive etherification. The stereochemistry in compound **5** was achieved from natural amino acids *L*– Phenyl alanine and *L*–valine.

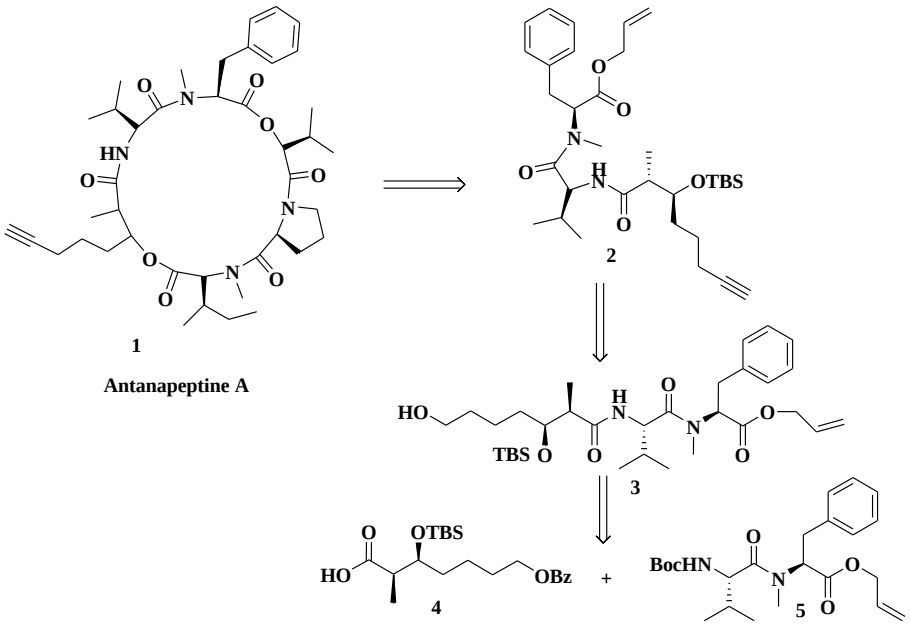

Figure 1. Retrosynthetic analysis of C1 – C24 fragment of Antanapeptin A

Preparation of acid 4: The synthesis began with Evans' aldol reaction of known aldehyde **7** using di-*n*-butylboron enolate of (*R*)-4-benzyl-3-propionyloxazolidin-2-one **6** to furnish the syn-product **8** in 83% yield (Figure 2). Exposure of **8** to TBSCl/Imidazole in CH_2Cl_2 at room temperature for 18 hours gave the TBS-ether **9** in 87% yield. Compound **9** was then treated with sodium borohydride in THF/pH 7 buffer at room temperature for the reductive removal of auxiliary to provide alcohol **10**. The primary hydroxyl group of compound **10** was oxidized to carboxylic acid using BAIB (bis acetoxy iodo benzene)/TEMPO (2,2,6,6-tetramethyl-1-piperidinyloxy free radical) in CH_2Cl_2/pH 7 buffer to obtain the acid fragment **4** in 89% yield.

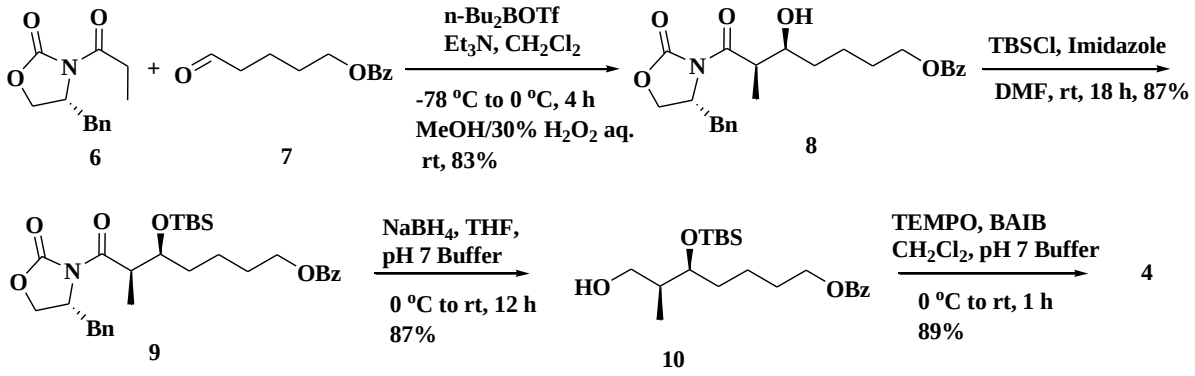

Figure 2. Synthesis of acid fragment **4**

Preparation of compound 5: The synthesis of compound **5** was commenced by carrying out the preparation of the known *N*-(*tert*-butoxycarbonyl)-*N*-methyl-*L*- Phenyl alanine **11** from *L*- Phenyl alanine using the literature procedure.[20] Esterification of acid **11** with allyl bromide was cleanly achieved by using K_2CO_3 in DMSO solvent at room temperature, to get the ester **12** in 80% yield. The required amide **5** was prepared from **12** by two transformations. Primarily, treating with TFA in CH_2Cl_2 to get secondary amine in good yields and the crude amine was used as such for the next step without further purification. Later, coupling of the free amine with (*tert*-butoxycarbonyl)-*L*-valine by using HATU/HOAT in CH_2Cl_2 at room temperature for 8 h to acquire the desired fragment **5** in 84% yield (Figure 3).[21-22]

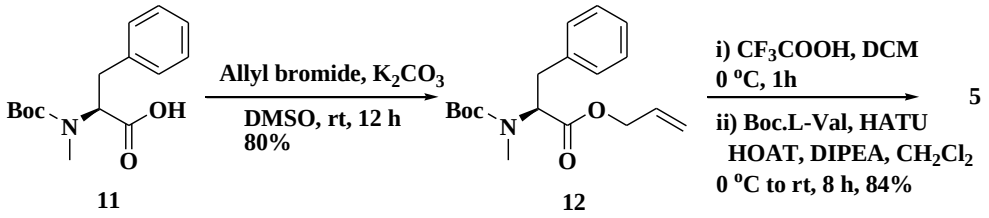

Figure 3. Synthesis of fragment **5**

Construction of C1 – C8 segment from 4 and 5: With successful completion of the desired fragments **4** and **5**, the attention was turned to couple them to give the diamide **13**. For that, intially the Boc protection of compound **5** was deprotected by using TFA in CH_2Cl_2 at 0 °C and then coupled with compound **4** under HATU/HOAT conditions at room temperature, to obtain the required product **13** in 85% yield . The resulting compound **13** was hydrolyzed with potassium carbonate in methanol to give the primary alcohol **3** in 75% yield which upon oxidation with TPAP/NMO to aldehyde followed by the addition of Ohira-Bestmann reagent gave the targeted terminal alkyne product **2** in 92% yield (Figure 4).

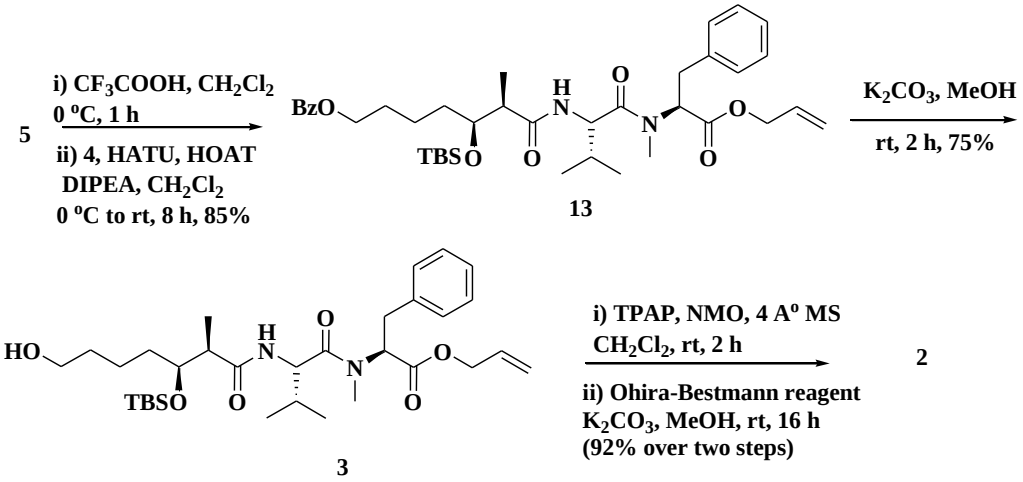

Figure 4. Construction of C1-C8 building block

3. Conclusions

In conclusion, a practical and stereoselective synthesis of C1-C24 fragment of Antanapeptin A having four stereo centers, two amide linkages, one ester linkage and with differential protective groups to allow further extensions was demonstrated, using Evans' Aldol reaction, TEMPO mediated oxidation, Ohira-Bestmann homologation as key transformations. Further investigation towards the total synthesis of Antanapeptin A are in progress.

4. Experimental Section

NMR spectra were recorded in $CDCl_3$ on brucker 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.

(5S,6R)-7-((R)-4-Benzyl-2-oxooxazolidin-3-yl)-5-hydroxy-6-methyl-7-oxoheptylbenzoate(8): To a stirred solution of acyl oxazolidinone **6**[20] (1.04 g 4.45 mmol) in CH_2Cl_2 (10 mL) was added drop wise *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 drop wise and the reaction was stirred at the same temperature for 1h. The mixture was cooled to -78 ^oC before a solution of aldehyde **7** (1.02 g, 4.95 mmol) in CH_2Cl_2 (15 mL) was added drop wise via cannula. Stirring was continued at -78 ^oC for 3 h before gradually warming to 0 ^oC. The reaction mixture was stirred for additional 3 h at 0 ^oC and then quenched by the addition of 0.1M pH 7 phosphate buffer (7.5 mL) followed by MeOH (10 mL) at 0 ^oC. After stirring for 5 min, a solution of 30% aqueous H_2O_2 (7.5 mL) in MeOH (15 mL) was added drop wise and stirred at the same temperature for 1h 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 **8** (1.63 g, 83%) as a viscous, color less 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, $CDCl_3$).

(5S,6R)-7-((R)-4-Benzyl-2-oxooxazolidin-3-yl)-5-(tert-butyldimethylsilyloxy)-6-methyl-7-oxoheptyl benzoate (9): To a stirred solution of **8** (1.60 g, 3.64 mmol) in DMF (15 mL) were added imidazole (0.8 g, 12.3 mmol) and TBSCl (*tert*-butylchlorodimethylsilane) (0.95 g, 7.4 mmol). After 18 h at 25 ^oC, 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 x 25 mL). The organic layer was dried over Na_2SO_4, filtered, concentrated in vacuo and distilled to yield **9** (1.74 g, 87%) as 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), 7.38 – 7.28 (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, $CDCl_3$).

(5S,6S)-5-(tert-Butyldimethylsilyloxy)-7-hydroxy-6-methylheptylbenzoate (10): To a stirred solution of **9** (1.70 g, 3.07 mmol) in THF (70 mL) at 0 ^oC was added a solution of $NaBH_4$ (0.58 g, 15.3 mmol) in pH 7 buffer (18.5 mL). The resulting solution was stirred for 10 min at 0 ^oC 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 1h. The separated aqueous phase was extracted with EtOAc (2 x 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 **10** (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.

(2R,3S)-7-(Benzoyloxy)-3-(tert-butyldimethylsilyloxy)-2-methylheptanoicacid (4): To a stirred solution of **10** (1.0 g, 2.62 mmol) in (5 mL) CH_2Cl_2 at 0 ^oC were added BAIB (3 g, 9.31 mmol), catalytic amount of TEMPO in pH 7 buffer (3 mL). The resulting solution was stirred for 10 min at 0 ^oC before being allowed to gradually warm to room temperature with stirring for 1h. The reaction was quenched by the addition of sat. aq. NH_4Cl (20 mL) and stirred at room temperature for 1h. The separated aqueous phase was extracted with EtOAc (2 x 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 **4 (**0.92 g, 89%) as 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.

(S)-allyl 2-(tert-butoxycarbonyl(methyl)amino)-3-phenylpropanoate (12): 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*– Phenylalanine (2.1 g, 12.3 mmol), in H_2O (20 mL) and THF (5 mL) at 0 ^oC. After the reaction mixture had been stirred at room temperature for 12h, it was neutralized with HCl (10%) until pH 2 has been reached. The mixture was then extracted with EtOAc (50 mL x 3), washed with brine, dried over Na_2SO_4. Concentration gave the crude *N*-Boc–phenylalanine (3.1 g, 100%). NaH (60 % in mineral oil, 2.45 g, 61.3 mmol) was added in portions to a solution of N- Boc–isoleucine (3.1 g, 11.69 mmol) and MeI (6.05 mL) in THF (50 mL) at 0 ^oC. After the reaction mixture had been stirred at room temperature for 36 h, it was poured in to saturated NH_4Cl solution (250 mL), extracted with EtOAc (3 x 150 mL) and dried over Na_2SO_4. Concentration gave *N*-methyl–*N*–Boc–phenylalanine (3 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 (3 g, 10.75 mmol) in DMSO (40 mL). After the mixture had been stirred at room temperature for 12h, it was portioned between EtOAc (75 mL) and brine (75 mL). The organic phase was separated and aqueous phase was extracted with EtOAc (2 x 100 mL). The combined organic phase was dried over Na_2SO_4 and concentrated. Flash chromatography gave **12** (3.2 g, 93.2%). IR ($CHCl_3$): ν 3065, 2936, 2880, 1741, 1701, 1602,1650, 1480, 1456, 1439,1393, 1367, 1313, 1255, 1183, 1145, 1047, 990, 931, 871, 773 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37 – 7.34(m, 3H), 7.23 (d, *J*= 8.2 Hz,1H) , 7.21 (d, *J* = 8.3 Hz,1H), 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), 4.36 (t, *J* = 11.9 Hz, 1H) , 3.29-3.13(m,2H) , 2.81 (s, 3H), 2.78* (s, 3H), 1.45 (m, 9H), ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 156.4, 135.2, 132.1,127.6,125.8,118.4, 80.3, 65.6, 59.6, 34.5, 30.8, 28.7; HRMS (ESI): *m*/*z* calculated for $C_{18}H_{26}O_4N$: $[M+H]^+$ 319.1784, found 319.1566. $[\alpha]_D^{25}$ = -34.7 (*c* 1.1, $CHCl_3$). *denotes the rotamer peak.

(S)-allyl2-((S)-2-(tert-butoxycarbonylamino)-N,3-dimethylbutanamido)-3phenylpropanoate (5): A solution of (*tert*-butoxycarbonyl)-*L*-valine acid (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 ^oC under N_2 atmosphere for 15 min, treated sequentially with salt [prepared from **12** (0.395 g, 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 x 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 **5** (0.46 g, 89%) as a colorless syrup. IR ($CHCl_3$): ν 3333, 3060, 2945, 2862, 1742, 1706, 1658, 1602, 1462,1439, 1367, 1294, 1178, 1001, 938, 876, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.34 (m, 3H), 7.23 (d, *J*= 8.2 Hz,1H) , 7.21(d, *J* = 8.3 Hz,1H), 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), 3.51- 3.55 (m, 2H), 3.09 (s, 2H), 2.10-1.89 (m, 2H), 1.50 (s, 9H), 1.00 – 0.80 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.5, 171.4, 136.4, 132.6, 128.2, 125.4, 127.7, 118.6, 79.8, 60.4, 55.3, 52.2, 31.4, 29.8, 19.8,; HRMS (ESI): *m*/*z* calculated for $C_{23}H_{34}N_2O_5Na$: $[M+Na]^+$ 441.2562, found 441.2458.

(5S,6R,9R,12S)-allyl-5-(4-(benzoyloxy)butyl)-12-benzyl-9-isopropyl-2,2,3,3,6,11hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate (13): A solution of acid **5** (0.51 g, 1.29 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 ^oC under N_2 atmosphere for 15 min, treated sequentially with TFA salt [prepared from **5** (0.45 g, 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 x 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 **13** (0.725 g, 85%) as a colorless syrup. IR ($CHCl_3$): ν 3342, 3333, 3233, 3060, 2926, 2915, 2854, 2840, 1701, 1667, 1651, 1609, 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), 7.36–7.32 (m, 3H), 7.23 (d, *J* = 8.2 Hz,1H) , 7.21(d, *J* = 8.3 Hz,1H) , 5.96 – 5.79 (m, 1H), 5.39-5.18 (m, 2H), 5.11 – 5.01 (m, 1H),4.69- 4.66 (m, 2H) , 4.65 – 4.54 (m, 2H), 4.34 – 4.27 (m, 3H), 3.82 – 3.68 (m, 3H) , 3.10- 3.05 (m, 2H) , 2.06 – 1.89 (m, 1H), 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 175.1, 171.2, 165.9, 136.5, 133.5, 132.5, 130.0, 129.4, 128.6, 125.9, 118.2, 73.5, 65.9, 56.7, 54.1, 49.2, 32.1, 30.1, 29.4, 26.2,19.2, 16.4, 14.4, -5.4. HRMS (ESI): *m*/*z* calculated for $C_{39}H_{58}N_2O_7SiNa$: $[M+Na]^+$ 717.4556, found 717.4214.

(5S,6R,9R,12S)-allyl-12-benzyl-5-(4-hydroxybutyl)-9-isopropyl-2,2,3,3,6,11-hexamethyl-7,10-dioxo-4-oxa-8,11-diaza-3-silatridecan-13-oate(3): To a stirred solution of **13** (0.70 g, 1.06 mmol) in MeOH (5 mL) was added K_2CO_3 (0.045 g, 0.33 mmol). The reaction was stirred at room temperature until complete by TLC (2h). 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 x 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 **3** (0.44 g, 75%) as a colorless syrup. IR ($CHCl_3$): ν 3640, 3300, 3233, 3100, 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}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34–7.32 (m, 3H), 7.22 (d, *J*= 8.2 Hz,1H) , 7.20(d, *J* = 8.3 Hz,1H) , 5.94 – 5.81 (m, 1H), 5.36 -5.28 (m, 2H), 5.11 – 5.01 (m, 1H), 4.65- 4.62 (m, 2H) , 4.60 – 4.54 (m, 2H), 4.45 (brs, 1H) , 4.31 – 4.26 (m, 3H), 3.82 – 3.68 (m, 3H) , 3.09 - 3.05 (m, 2H) , 2.05 – 1.89 (m, 1H), 1.32 – 1.19 (m, 4H), 1.19 -1.07 (m, 1H), 1.05-0.83 (m, 19H), 0.10 – 0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 174.3, 171.2, 136.6, 132.5,128.6,118.2, 74.5, 66.0, 65.3, 62.8, 58.2, 54.1, 49.2, 38.0, 34.2, 32.1, 26.2, 25.1, 19.2, 16.4, 14.4, -5.4; HRMS (ESI): *m*/*z* calculated for $C_{32}H_{54}N_2O_6SiNa$: $[M+Na]^+$ 613.3914, found 613.3812.

(5S,6R,9R,12S)-allyl-12-benzyl-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(2): To a stirred solution of 3 (0.42 g, 0.755 mmol) and powdered 4 A^0 molecular sieves (0.65 g) in CH_2Cl_2 (15 mL) were subsequently added 4-methylmorpholine–*N*–Oxide (0.23 g, 1.94 mmol) and tetrapropylammonium perruthenate (0.023 g, 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 aldehyde as a colorless oil. The residue was placed under high vaccum for 2 h before being used in the

subsequent reaction without purifiation. Stirred the aldehyde, K_2CO_3 and the Ohira-Bestmann reagent (0.26 g, 1.32 mmol) 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 x 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 **2** (0.35 g, 92%) as yellow syrup. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 –7.34 (m, 3H), 7.26 (d, *J* = 8.2 Hz,1H) , 7.25 (d, *J* = 8.3 Hz,1H) , 5.94 – 5.81 (m, 1H), 5.36 -5.28 (m, 2H), 5.11 – 5.01 (m, 1H), 4.65- 4.62 (m, 2H) , 4.60 – 4.54 (m, 2H), 4.31 – 4.26 (m, 3H), 3.82 – 3.68 (m, 3H) , 2.20 (m, 1H) , 2.05 – 1.89 (m, 1H), 1.32 – 1.19 (m, 4H), 1.19 -1.07 (m, 1H), 1.05-0.83 (m, 19H), 0.10 – 0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ172.1, 132.3, 136.8, 128.5, 127.8,125.9, 118.5, 83.9, 71.5, 68.2, 65.9, 56.5, 52.1, 48.2, 38.1, 34.7, 32.1, 31.4, 26.2, 18.7, 16.4, -5.4; HRMS (ESI): *m*/*z* calculated for $C_{33}H_{52}N_2O_5SiNa$: $[M+Na]^+$ 607.3140, found 607.3120.

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