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Ionic-Liquid-Supported Total Synthesis of Sansalvamide A Peptide

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Abstract: A facile and efficient total synthesis of bioactive sansalvamide A peptide has been accomplished, including the-ionic-liquid supported method and final PyBOP-promoted ring closure.

Keywords: ionic liquid, sansalvamide A peptide, total synthesis

INTRODUCTION

Sansalvamide A (San A, **1**) is a cyclic depsipeptide, isolated from organic extracts of the mycelium of a fungus of the genus *Fusarium* collected from the surface of the seagrass *Halodule wrightii*.[1] It showed a mean IC_{50} value of 27.4 μg/mL against the National Cancer Institute's 60-cell-line panel and an in vitro IC_{50} value of 9.8 μg/mL toward HCT-116 colon carcinona.[1,2] This natural product was found to inhibit virus-encoded type-1 topoisomerase, which is likely to be required for molluscum contagiosum

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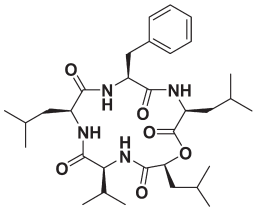
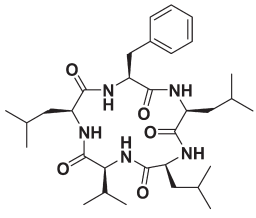
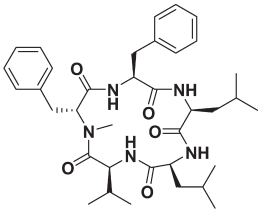
virus (MCV) replication.[3] Silverman's group reported the solid-phase-supported synthesis of the corresponding cyclic peptide of San A (**2**), as well as its *N*-methyl derivatives.[2,4] Styers et al. reported several San A derivatives that demonstrated promising anticancer properties,[5] and compound **3** demonstrates IC_{50} values of 0.80 μM for HCT-116 and 0.65 μM for HCT-15, which are much more potent than San A peptide **2** and 5-fluorouracil against two microsatellite-unstable (MSI) colon-cancer cell lines (HCT-116 and HCT-15).[5d]


Compound 1


Compound 2

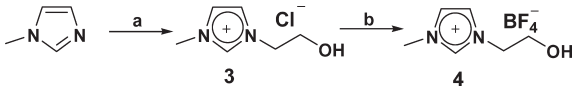

Compound 3

Silverman's group synthesized San A peptide and derivatives using a solid phase,[4] whereas Styers et al. employed the strategy of solution-phase synthesis.[5b] The two approaches have different characteristics. Cyclic peptides such as San A peptide derivatives show good inhibitory activities against several different tumor cell lines.[2,5] Therefore, we want to develop a new and potentially rapid synthesis approach that combines the advantages of the two current methods, such as high loading capacity, low excess reagent, facile purification, routine spectroscopic analysis, and relatively low cost.

Recently, more attention has been paid to functionalized ionic liquids (ILs) at room temperature as environmentally benign reaction media because of their intriguing properties, including good solvability, high thermal and chemical stability, negligible vapor pressure, and ionic conductivity. Numerous chemical reactions, such as Diels–Alder reactions,[6] hydrogenation reactions,[7] Heck reactions,[8] Meerwein reactions,[9] and some enzymatic reactions,[10] have been mediated by ionic liquids. In recent years, ionic-liquid-supported methods have been developed as efficient and useful approaches for the synthesis of oligosaccharides[11] and pentapeptides[12] and also have been applied to synthesize useful chemical intermediates.[13,14] Herein, we describe an efficient ionic-liquid-supported synthesis of the cyclic San A peptide.

RESULTS AND DISCUSSION

The functional ionic liquid, using as a support for the synthesis of San A peptide, was synthesized as shown in Scheme 1. Treatment of *N*-methylimidazole with chlorohydrin under microwave irradiation obtained the ionic liquid



3 4

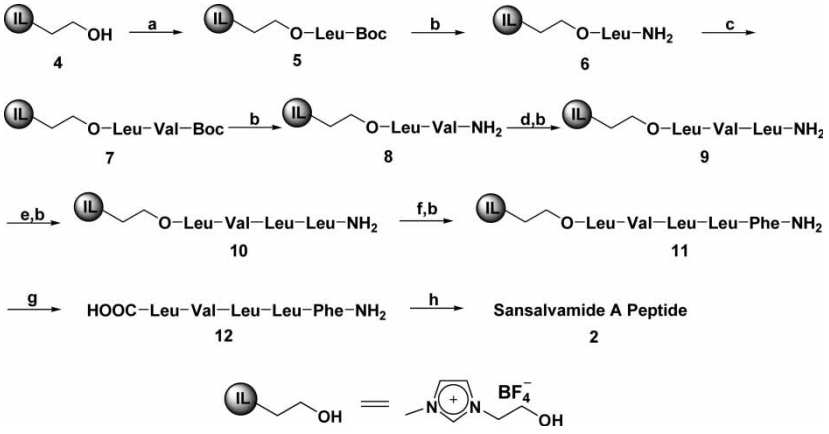
Scheme 1. Reagents and conditions: (a) chlorohydrin (1 equiv), N_2, microwave 120°C, 5 min; (b) $NaBF_4$ (2 equiv), CH_3CN, 80°C, 24 h.

3,[13] which was then converted to 3-hydroxyethyl-(1-methylimidazolium)-tetrafluoroborate **4** by anion exchange.

In the loading procedure, ionic liquid support **4** was treated with Boc-Leu-OH, N,N′-dicyclohexylcarbodiimide (DCC), and 4-dimethylaminopyridine (DMAP) in dry CH_3CN at room temperature under nitrogen. After the mixture was filtrated and concentrated, the crude residue was washed with ether, dissolved in CH_2Cl_2, washed with 2 M HCl, dried, and concentrated to afford ionic-liquid-supported Leu-Boc **5**.[12] Compound **5** deprotected the Boc group with trifluoroacetic acid (TFA) in dry CH_2Cl_2 at room temperature under nitrogen. After concentration of the reaction mixture, the residue was washed with ether and then gave ionic-liquid-supported Leu-NH_2 **6**. Compound **6** was reacted with Boc-Val-OH in the presence of diisopropylethylamine (DIPEA) and a highly effective activating reagent, benzotriazole-1-yl-oxy trispyrrolidinophosphonium hexafluorophosphate (PyBOP), in dry CH_3CN at 35°C under nitrogen. Then resulting reaction mixture was concentrated and washed in the same procedure as compound **5** to afford ionic-liquid-supported Leu-Val-Boc **7.** After deprotection of the Boc group of **7** and washing, the ionic-liquid-supported peptides were extended through the same set of conditions for coupling reaction, washing, deprotection, and washing as before, using Boc-Leu-OH, Boc-Leu-OH, and Boc-Phe-OH successively in the peptide elongation as shown in Scheme 2. Then the linear pentapeptide **11** was released from the ionic liquid support using 1 M aqueous sodium hydroxide and cyclized using PyBOP to afford cyclic peptide **2.**

In experimentation, it was found that the linear ionic-liquid-supported peptides are soluble in polar organic solvents such as acetonitrile, methanol, acetone, and dichloromethane but are not soluble in ether. Additionally, the undesired by-products and excessive raw material can be washed out by ether and water after each of the coupling and deprotection reactions, and the obtained ionic-liquid-supported peptides were pure enough to react to the next Boc-protected amino acid without further chromatographic purification. All the intermediates of ionic-liquid-supported peptides could be confirmed with ^1H NMR and mass spectra (MS). An important advantage of the strategy outlined here is that the cation of ionic-liquid-supported peptides **5**–**11** could be detected easily as the most intense peak in the MS obtained by electrospray ionization (ESI) as shown in Table 1.

A survey of different reaction conditions was carried out in the ring-closure step, and the results are summarized in Table 2. Direct cyclization



Scheme 2. Reagents and conditions: (a) DCC (2 equiv), DMAP (0.4 equiv), dry CH_3CN, N_2, rt, 18 h; (b) 40% TFA in CH_2Cl_2, N_2, rt, 40 min; (c) Boc-Val-OH (1.5 equiv), PyBOP (1.2 equiv), DIPEA (3 equiv), dry CH_3CN, N_2, 35°C, 12 h; (d) Boc-Leu-OH (1.5 equiv), PyBOP (1.2 equiv), DIPEA (3 equiv), dry CH_3CN, N_2, 35°C, 12 h; (e) Boc-Leu-OH (1.5 equiv), PyBOP (1.2 equiv), DIPEA (3 equiv), dry CH_3CN, N_2, 35°C, 12 h; (f) Boc-Phe-OH (1.5 equiv), PyBOP (1.2 equiv), DIPEA (3 equiv), dry CH_3CN, N_2, 35°C, 12 h; (g) NaOH (1 equiv), THF/H_2O (1:1, v/v), rt, 6 h; (h) PyBOP (5 equiv), DIPEA (15 equiv), NMP, N_2, rt, 24 h.

of **11** was first attempted using HBTU in DMF at room temperature, in the presence of DIPEA. No product was detected after 3 days. Other reaction conditions were altered, such as changing the solvent or raising the temperature to 35°C, and still no product was found. The peptide **2** was achieved from ionic-liquid-supported peptide **11** in one step, by using NaOH to cleave ionic liquid support, and then cyclization by adding PyBOP directly to the reaction mixture. However, the yield turned out to be low, with only 5% of crude

Table 1. Ionic-liquid-supported synthesis of cyclic peptide sansalvamide A

Entry	Products	ESI found (100%)	Yields (%)
1	**5**	$M^+ = 340.1$	70
2	**6**	$2M^+ + BF_4^- = 566.9$	98
3	**7**	$M^+ = 439.2$	92
4	**8**	$M^+ = 339.2$	96
5	**9**	$M^+ = 452.3$	87[a]
6	**10**	$M^+ = 565.4$	89[a]
7	**11**	$M^+ = 712.5$	87[a]
8	**12**	$M + 1 = 604.2$	60

[a]Yields of two steps.

Table 2. Methods investigated for cyclization of the linear peptide

Entry	Precursors	Reagents	Conditions[c]	Yields (%)
1	**11**	HBTU (5 equiv)/DIPEA	DMF/rt/3 days	no product
2	**11**	HBTU (5 equiv)/DIPEA	THF/35°C/24 h	no product
3	**11**	PyBOP (5 equiv)/ DIPEA	CH_3CN/35°C/24 h	no product
4	**11**[a]	PyBOP (5 equiv)/NaOH	NMP, CH_3CN/35°C/ 24 h	5
5	**12**[b]	HATU (5 equiv)/ DIPEA	DMF/rt/24 h	23
6	**12**	PyBOP (5 equiv)/ DIPEA	NMP/rt/24 h	51
7	**12**	PyBOP (5 equiv)/ DIPEA	DMF, CH_2Cl_2/rt/24 h	10

[a]First NaOH was used to cleave away ionic liquid, and then PyBOP was added directly.

[b]Raw material **12** was the crude product without purification.

[c]All reactions were performed under nitrogen.

product. The linear pentapeptide **12** was prepared by cleaving the ionic liquid support with 1 M aqueous sodium hydroxide in THF/H_2O,[12] and methods other than direct cyclization were investigated to increase the yield of the cyclization step. Three cyclization conditions were used to prepare peptide **2** from **12** as listed in Table 2. The condition of using PyBOP in the presence of DIPEA in NMP provided the highest yield (51%) among all the methods. The desired cyclic peptide **2** was purified using reverse phase high performance liquid chromatography (HPLC) and confirmed via liquid chromatography tandem mass spectrometry (LC/MS).

Compared with the reported solid-phase synthesis of San A peptide,[4] the loading step of ionic-liquid-supported synthesis is more facile with only one step, relatively lower costs, and higher loading capacity. Additionally, the intermediates could be detected by routine spectroscopic analysis. Compared with the reported solution-phase synthesis of San A peptide,[5a,5b] more facile purification is achieved by ionic liquid strategy, and the final PyBOP-promoted ring-closure is a time-saving protocol, which reduced the reaction time from 4 days[5a] to 24 h with the same yields.

In summary, we have demonstrated the application of ionic liquid for the synthesis of bioactive cyclic peptide San A. It is noteworthy that the strategy achieved high loading capacity and had simple purification of intermediates using only sequential ether and aqueous washing. This approach is a proof of principle for the synthesis of cyclic peptides in an efficient and potentially fast way. Further studies of other cyclic peptides and improvements of the strategy are in progress.

EXPERIMENTAL

The reagents (chemicals) were purchased from Shanghai Chemical Reagent Company, Lancaster, and Acros and were used without further purification. Yields were not optimized. Nuclear magnetic resonance (NMR) spectra were recorded on a Brucker AMX-300 NMR (TMS as internal standard). Chemical shifts were reported in parts per million (ppm, δ) downfield from tetramethylsilane. Proton coupling patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad (br). Low- and high-resolution mass spectra (LRMS and HRMS) were obtained by electrospray ionization (ESI) produced by a LCQ-DECA spectrometer.

Preparation of 1-(2-Hydroxyethyl)-3-methylimidazolium Chloride 3

A mixture of 1-methylimidazole (2.06 g, 0.025 mol) and chlorohydrin (2.01 g, 0.025 mol) was placed in a 20-mL microwave vial, and the vial was sealed after filling with nitrogen. The mixture was then irradiated for 5 min at 120°C. After the reaction was cooled to ambient temperature, the formed viscous solid was washed successively with ether (10 mL × 3), and then dried at 50°C under vacuum for 4 h. The hydroxyl-functionalized ionic liquid **3** was obtained as white crystals (3.98 g, 98%). ^{1}H NMR (300 MHz, D_2O): δ 3.99 (s, 3H), 4.01 (t, $J = 3.6$ Hz, 2H), 4.40 (t, $J = 3.9$ Hz, 2H), 7.54 (s, 1H), 7.60 (s, 1H), 8.84 (s, 1H).

Preparation of 1-(2-Hydroxyethyl)-3-methylimidazolium Tetrafluoroborate 4

A mixture of 1-(2-hydroxyethyl)-3-methylimidazolium chloride (3.98 g, 0.024 mol), $NaBF_4$ (5.28 g, 0.048 mol), and dry acetonitrile (40 mL) was heated to reflux with stirring for 25 h under nitrogen. Upon cooling, the white precipitate was filtered off and washed with acetonitrile (10 mL × 2). Concentration of the combined filtrates gave product **4** as a light yellow oil (4.88 g, 95%). ^{1}H NMR (300 MHz, acetone-d_6) δ 3.70 (t, $J = 5.1$ Hz, 2H), 3.85 (s, 3H), 4.19 (t, $J = 5.1$ Hz, 2H), 7.68 (s, 1H), 7.69 (s, 1H), 9.02 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 127.1, $[M]^-$ (100%): 87.1.

Preparation of the Ionic-Liquid-Support Boc-Leucine 5

A mixture of ionic liquid **4** (3.10 g, 14 mmol), Boc-Leu-OH·H_2O (7.21 g, 28 mmol), dicyclohexylcarbodiimide (5.97 g, 28 mmol), and dimethylaminopyridine (0.71 g, 5.6 mmol) was added in dry acetonitrile (40 mL) and dry dichloromethane (10 mL). The mixture was stirred vigorously for 18 h at

room temperature under nitrogen. After filtration through a plug of celite®, the Celite plug was washed with acetonitrile, and the combined organic phase was concentrated in vacuum. The residue was washed with ether (30 mL × 3), then dissolved in CH_2Cl_2 and washed with 2M HCl (10 mL × 3). The organic phase was dried over Na_2SO_4 and concentrated to give ionic-liquid-supported Boc-Leu **5** 4.32 g (70%) as a pale yellow oil. ^{1}H NMR (300 MHz, acetone-d_6) δ 0.86–0.92 (m, 6H), 1.40 (s, 9H), 1.51–1.58 (m, 3H), 4.07 (s, 3H), 4.15–4.20 (m, 1H), 4.40–4.58 (m, 2H), 4.60–4.66 (m, 2H), 6.41 (br, 1H), 7.73 (s, 1H), 7.83 (s, 1H), 9.12 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 340.1.

General Procedure for the Deprotection and Coupling Reactions of Ionic Supported Peptides 6–11

A solution of ionic-liquid-supported Boc-peptide (6 mmol) was treated with 40% TFA in dry CH_2Cl_2 (25 mL) for 1 h at room temperature under nitrogen. After concentration of the reaction mixture, the residue was washed with ether (20 mL × 3) and dried at 35°C under vacuum line to give the deprotected ionic-liquid-supported peptide as TFA salt. Then DIPEA (18 mmol), was added dropwise into the mixture of ionic-liquid-supported peptide TFA salt, the next Boc-protected amino acid (9 mmol), and PyBOP (7.2 mmol) in dry CH_3CN (40 mL). The resulting reaction mixture was stirred at 35°C under nitrogen for 12 h. After evaporation in vacuum, the residue was washed with ether (30 mL × 3), then dissolved in CH_2Cl_2 and washed with water (10 mL × 3). The organic phase was dried over Na_2SO_4 and concentrated to afford the ionic-liquid-supported Boc-peptide.

Characteristic Data for 6–11

Ionic-liquid-supported Leu-NH_2 6: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.91–0.93 (m, 6H), 1.81–1.83 (m, 3H), 4.01 (s, 3H), 4.21–4.27 (m, 1H), 4.58–4.76 (m, 4H), 7.67 (s, 1H), 7.82 (s, 1H), 9.15 (s, 1H); MS (ESI): m/z $[2M^+ + BF_4^-]$ (100%): 566.9.

Ionic-liquid-supported Leu-Val-Boc 7: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.85–0.93 (m, 12H), 1.40–1.43 (m, 12H), 1.55–1.71 (m, 3H), 4.07 (s, 3H), 4.38–4.49 (m, 2H), 4.61–4.69 (m, 3H), 7.70 (s, 1H), 7.81 (s, 1H), 9.11 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 439.2.

Ionic-liquid-supported Leu-Val-NH_2 8: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.87–0.92 (m, 6H), 1.05–1.11 (m, 6H), 1.41–1.45 (m, 3H), 1.52–1.72 (m, 3H), 4.07 (s, 3H), 4.43–4.51 (m, 2H), 4.68–4.75 (m, 3H), 7.72 (s, 1H), 7.83 (s, 1H), 9.16 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 339.2.

Ionic-liquid-supported Leu-Val-Leu-Boc: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.85–0.93 (m, 16H), 1.41–1.45 (m, 15H), 1.55–1.65 (m, 4H), 4.10 (s, 3H), 4.43–4.51 (m, 2H), 4.37–4.41 (m, 1H), 4.51–4.58 (m, 1H), 4.69–4.71 (m, 2H), 7.70 (s, 1H), 7.82 (s, 1H), 9.13 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 552.3.

Ionic-liquid-supported Leu-Val-Leu-NH$_2$ 9: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.83–0.98 (m, 16H), 1.36–1.38 (m, 6H), 1.54–1.68 (m, 3H), 1.79–1.83 (m, 1H), 4.03 (s, 3H), 4.26–4.50 (m, 4H), 4.60–4.63 (s, br, 2H), 7.65 (s, 1H), 7.76 (s, 1H), 9.02 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 452.3.

Ionic-liquid-supported Leu-Val-Leu-Leu-Boc: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.85–0.95 (m, 24H), 1.19–1.43 (m, 16H), 1.56–1.76 (m, 8H), 3.12–3.18 (m, 3H), 4.06 (s, 3H), 4.20–4.25 (m, 1H), 4.43–4.60 (m, 1H), 4.61–4.78 (m, 1H), 7.68 (s, 1H), 7.80 (s, 1H), 9.08 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 665.4.

Ionic-liquid-supported Leu-Val-Leu-Leu-NH$_2$ 10: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.84–0.96 (m, 24H), 1.39–1.45 (m, 7H), 1.61–1.67 (m, 6H), 1.79–1.84 (m, 2H), 3.20 (s, br, 3H), 4.08 (s, 3H), 4.22–4.29 (m, 2H), 4.35–4.42 (m, 1H), 4.52–4.70 (m, 2H), 7.70 (s, 1H), 7.80 (s, 1H), 9.10 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 565.4.

Ionic-liquid-supported Leu-Val-Leu-Leu-Phe-Boc: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.84–1.01 (m, 24H), 1.33–1.40 (m, 17H), 1.55–1.71 (m, 5H), 1.96 (s, 1H), 3.50 (s, br, 5H), 4.08 (s, 3H), 4.14–4.19 (m, 1H), 4.30–4.39 (m, 3H), 4.50–4.56 (m, 2H), 7.18–7.32 (m, 5H), 7.59 (s, 1H), 7.78 (s, 1H), 9.06 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 812.7.

Ionic-liquid-supported Leu-Val-Leu-Leu-Phe-NH$_2$ 11: ^{1}H NMR (300 MHz, acetone-d_6) δ 0.83–0.95 (m, 23H), 1.38–1.43 (m, 8H), 1.62–1.71 (m, 5H), 1.79–1.81 (m, 1H), 3.13–3.35 (m, 5H), 4.06 (s, 3H), 4.52–4.55 (m, 5H), 7.27–7.37 (m, 5H), 7.67 (s, 1H), 7.77 (s, 1H), 9.11 (s, 1H); MS (ESI): m/z $[M]^+$ (100%): 712.5.

Procedure for the Cleavage of Ionic-Liquid Supported Reaction

The ionic-liquid-supported pentapeptide **11** (200 mg, 0.25 mmol) was dissolved in THF/H_2O (1:1, v/v, 4.0 ml), followed by the addition of 1M NaOH aqueous solution (0.25 mL), and stirred at room temperature for 6 h. After evaporation in vacuum, the residue was acidified to pH 5–6. The precipitate was collected by filtration, washed with distilled water, and dried on the vacuum line to give linear pentapeptide **12** (91 mg, 60%). ^{1}H NMR (300 MHz, CD_3OD): δ 0.86–0.97 (m, 24H), 1.28–1.39 (m, 2H), 1.53–1.70 (m, 8H), 2.00–2.05 (m, 1H),

2.93–3.01 (m, 1H), 4.07–4.14 (m, 1H), 4.35–4.52 (m, 4H), 7.26–7.38 (m, 5H); MS (ESI): m/z $[M + 1]^+$ (100%): 604.3.

Procedure for Cyclization

DIPEA (353 μL, 2.14 mmol) was added dropwise to a solution of pentapeptide **12** (86 mg, 0.14 mmol) and PyBOP (375 mg, 0.71 mmol) in NMP (5 mL). The reaction mixture was stirred for 24 h at room temperature under nitrogen. The mixture was diluted with 100 mL of CH_2Cl_2 and 20 mL of H_2O. The organic phase was then washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, filtrated, and concentrated under reduced pressure to yield the crude product (58 mg, 51%). The desired cyclic peptide **2** was then purified using reverse-phase HPLC and confirmed via LC/MS. ^{1}H NMR (300 MHz, CD_3OD): δ 0.85–0.99 (m, 24H), 1.38–1.41 (m, 1H), 1.42–1.49 (m, 3H), 1.57–1.82 (m, 6H), 2.33–2.36 (m, 1H), 3.16–3.21 (m, 2H), 3.63–3.66 (d, $J = 9.3$ Hz, 1H), 4.06 (m, 1H), 4.19–4.34 (m, 3H), 7.21–7.24 (m, 5H); ^{13}C NMR (75 MHz, CD_3OD): δ 19.9, 20.4, 22.3, 22.4, 22.8, 23.4, 23.7, 23.8, 26.51, 26.57, 26.8, 31.0, 37.6, 41.1, 41.6, 41.7, 55.4, 55.8, 56.0, 58.7, 64.4, 128.3, 130.0, 130.7, 139.0, 173.8, 174.4, 174.8, 174.9, 175.1; HRMS (ESI) m/z $[M + Na]^+$ calcd. for $C_{32}H_{51}N_5O_5Na$ 608.3788; found 608.3823.

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