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Synthesis and cytotoxicity of aurilide analogs

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ABSTRACT

The artificial analogs of aurilide (**1**), a potent cytotoxic cyclodepsipeptide of marine origin, were synthesized, and the structure–activity relationships were investigated.

Aurilide (**1**) is a 26-membered cyclodepsipeptide, isolated from the Japanese sea hare *Dolabella auricularia*,[1] which exhibited potent cytotoxicity against HeLa S_3 cells with an IC_{50} value of 11 ng/mL.[2] We achieved enantioselective synthesis of aurilide and examined its biological activities by using synthetic specimens. The NCI's human cancer cell panel showed that aurilide (**1**) exhibited a high level of cytotoxicity, and that **1** is selectively active against lung, ovarian, renal, and prostate cancer cell lines. Aurilide (**1**) showed unusually high in vivo antitumor activity in the NCI's hollow fiber assays and expected as a promising candidate for cancer treatment. Recently, several natural products such as aurilides B and C,[3] kulokekahilide-2,[4] and palau'amide[5] structurally related to **1** have been isolated. The target biomolecule of **1** and related compounds, however, remains to be clarified. To design the probe molecule for searching the target biomolecule of **1**, studies on the structure–activity relationships in **1** are needed. In this paper, we reported synthesis of artificial aurilide analogs and their cytotoxicity against HeLa S_3 cells.

Amino group is useful for connecting functional molecule such as biotin, so we attempted to synthesize the analogs **4**, **5**, and **6** with Lys residue. We also planned to synthesize analog **7** with protected amino group and analog **8** with carboxyl group, which have a linker. To investigate the effect of hydroxyl group of **1** for cytotoxicity, synthesis of deoxyaurilide (**3**) was planned (see Fig. 1).

Synthesis of **3** began with dehydration of alcohol **10**,[2] a synthetic intermediate of aurilide (**1**) (Scheme 1). Treatment of **10** with ArSeCN and Bu_3P gave α,β,γ,δ-unsaturated ester, selective hydrogenation of which afforded an α,β-unsaturated ester. Hydrolysis of the α,β-unsaturated ester gave carboxylic acid **11**. Condensation between **11** and **12** afforded ester **13**, which was transformed into deoxyaurilide (**3**)[6] by 4-step reactions including esterification with *N*-Me-Ala and macrolactamization.

Analog **4** was synthesized from alcohol **14**[2] (Scheme 2). Esterification of **14** with protected Lys followed by macrolactamization and removal of MTM protecting group gave analog **4**.

Synthesis of **5** started from tetrapeptide **15**[2] (Scheme 3). Cleavage of the ^{t}Bu ester group in **15** followed by condensation with protected Lys provided pentapeptide **16**. Esterification of **16** with **17** and subsequent similar sequence of reactions as described above afforded analog **5**.

Analog **6** was synthesized from dipeptide **18**[2]) (Scheme 4). Removal of the Z group in **18** followed by condensation[7] with protected Lys provided tripeptide **19**. Tripeptide **19** was condensed with isoleucic acid at N-terminus and with Val at C-terminus, respectively, to give pentapeptide **20**, which was transformed into analog **6**.

Acylation[8] of aurilide (**1**) gave analog **7**, which was converted into analog **8**.[9] Analog **9** was prepared from 6-*epi*-aurilide (**2**) in the same manner as described above.

The cytotoxicity of aurilide and the artificial analogs against HeLa S_3 cells is summarized in Table 1. Deoxyaurilide (**3**) was slightly less cytotoxic than aurilide (**1**), which indicated that the hydroxyl group of **1** is not so significant for the strong

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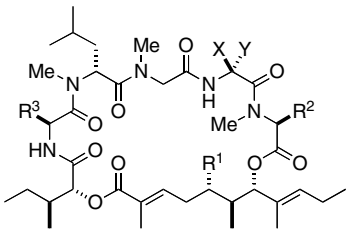
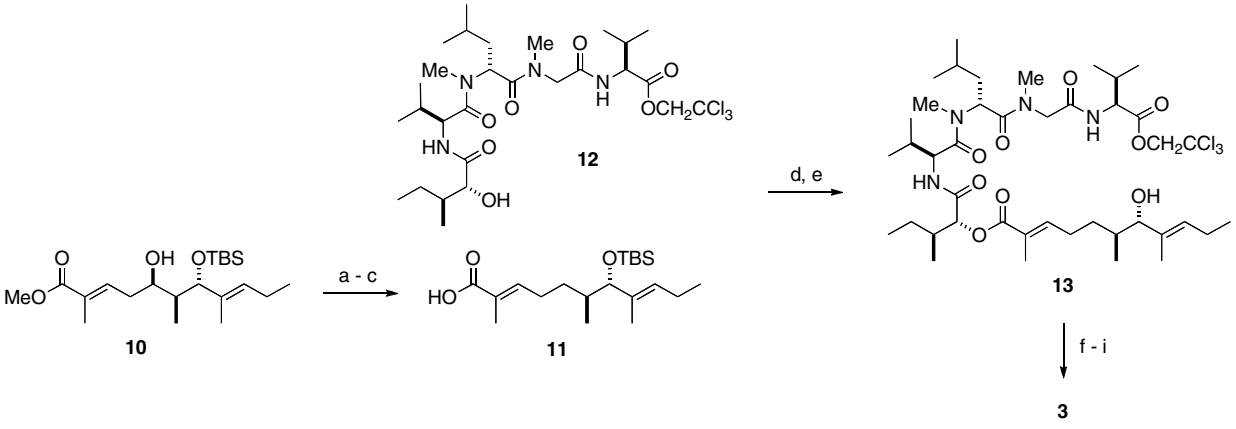
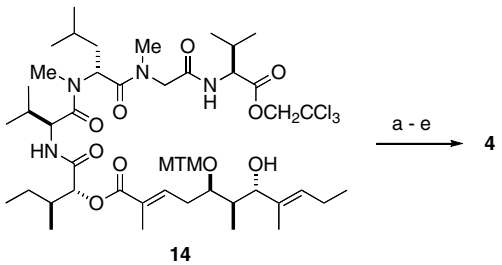


	R^1	R^2	R^3	X	Y
aurilide (**1**)	OH	Me	^{i}Pr	^{i}Pr	H
2	OH	Me	^{i}Pr	H	^{i}Pr
3	H	Me	^{i}Pr	^{i}Pr	H
4	OH	$(CH_2)_4NHBoc$	^{i}Pr	^{i}Pr	H
5	OH	Me	^{i}Pr	$(CH_2)_4NHBoc$	H
6	OH	Me	$(CH_2)_4NHBoc$	^{i}Pr	H
7	$OCO(CH_2)_5NHFmoc$	Me	^{i}Pr	^{i}Pr	H
8	$OCO(CH_2)_5NHCO(CH_2)_2CO_2H$	Me	^{i}Pr	^{i}Pr	H
9	$OCO(CH_2)_5NHCO(CH_2)_2CO_2H$	Me	^{i}Pr	H	^{i}Pr

Figure 1. Structures of aurilide (**1**) and its artificial analogs.



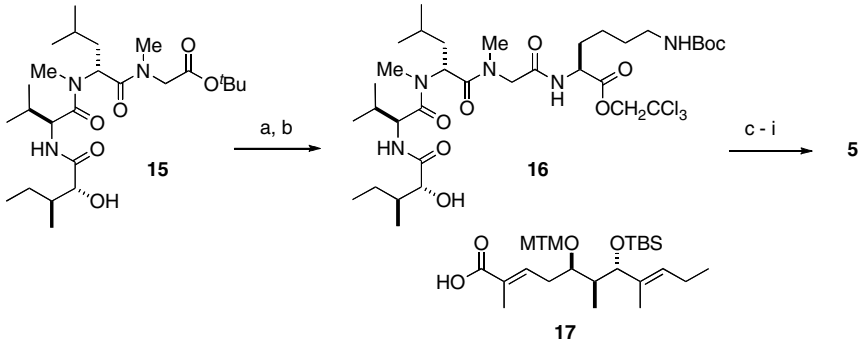
Scheme 1. Reagents and conditions: (a) *o*-$NO_2C_6H_4SeCN$, Bu_3P, THF, rt, 83%; (b) H_2, Lindlar's cat., quinoline, EtOAc, rt, 62%; (c) 5 M LiOH aq, MeOH, rt, 95%; (d) EDCI·HCl, DMAP, CH_2Cl_2; (e) HF·Py, pyridine, rt, 36% in 2 steps from **11**; (f) Fmoc-*N*-Me-L-Ala, EDCI·HCl, DMAP, CH_2Cl_2, rt, 51%; (g) Zn, NH_4OAc aq, rt; (h) Et_2NH, CH_3CN, rt; (i) EDCI·HCl, HOAt, CH_2Cl_2-DMF, rt, 25% in 3 steps. EDCI = 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide, Fmoc = 9-fluorenylmethyloxycarbonyl, HOAt = 1-hydroxy-7-azabenzotriazole.



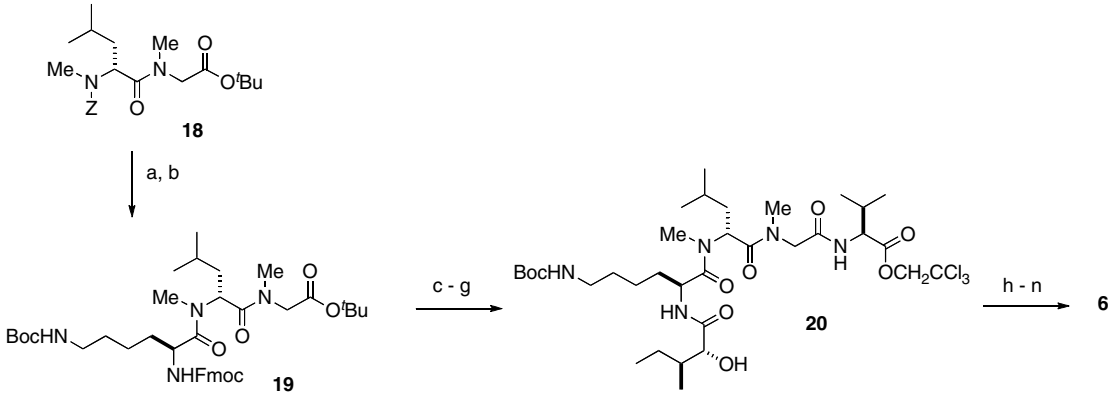
Scheme 2. Reagents and conditions: (a) ε-Boc-α-Fmoc-*N*-Me-L-Lys, EDCI·HCl, DMAP, CH_2Cl_2, 88%; (b) Zn, NH_4OAc aq, rt; (c) Et_2NH, CH_3CN, rt; (d) EDCI·HCl, HOAt, CH_2Cl_2-DMF, rt; (e) $AgNO_3$, 2,6-lutidine, THF-H_2O, 70 °C, 17% in 4 steps.

cytotoxicity of **1**. Although analogs **4** and **6** that possess protected amino group were also slightly less cytotoxic than **1**, the activity of these analogs are enough to use as the probe molecules for searching target biomolecule. Analogs **5**, **7**, and **8** were ca 100-fold less cytotoxic than **1**, but these analogs still showed considerable activity (less than 1 μg/mL). Therefore, analogs **5**, **7**, and **8** are also useful for further research. Since the analog **9** prepared from 6-*epi*-aurilide (**2**) has no cytotoxicity, it is useful as a negative probe.

In conclusion, we synthesized the artificial analogs of aurilide, a potent cytotoxic cyclodepsipeptide, and investigated structure–activity relationships. Several analogs were found to be useful as the probe molecules for searching target biomolecule. Further



Scheme 3. Reagents and conditions: (a) TMSOTf, 2.6-lutidine, 0 °C; (b) ε-Boc-L-Lys-OCH_2CCl_3, EDCI·HCl, HOBt, DMF-CH_2Cl_2, rt, 54% in 2 steps; (c) EDCI·HCl, DMAP, CH_2Cl_2, rt; (d) HF·Py, pyridine, rt, 32% in 2 steps from **17**; (e) Fmoc-*N*-Me-L-Ala, EDCI·HCl, DMAP, CH_2Cl_2, rt, 66%; (f) Zn, NH_4OAc aq, rt; (g) Et_2NH, CH_3CN, rt; (h) EDCI·HCl, HOAt, CH_2Cl_2-DMF, rt; (i) $AgNO_3$, 2,6-lutidine, THF-H_2O, 70 °C, 70% in 4 steps. HOBt = 1-hydroxybenzotriazole.



Scheme 4. Reagents and conditions: (a) H_2, Pd-C, EtOH, rt; (b) ε-Boc-α-Fmoc-L-Lys, PyBOP,[7] $^{i}Pr_2NEt$, CH_2Cl_2, rt, 100% in 2 steps; (c) Et_2NH, CH_3CN, rt; (d) sodium salt of allo-D-isoleucic acid, EDCI·HCl, HOBt, DMF, rt, 98% in 2 steps; (e) TMSOTf, 2,6-lutidine, 0 °C; (f) $(Boc)_2O$, 1 M NaOH aq, rt; (g) L-Val-OCH_2CCl_3, HOBt, Et_3N, DMF, CH_2Cl_2, rt, 76% in 3 steps; (h) **17**, EDCI·HCl, DMAP, CH_2Cl_2, rt, 74%; (i) HF·Py, pyridine, 40 °C, 78%, (j) Fmoc-*N*-Me-L-Ala, EDCI·HCl, DMAP, CH_2Cl_2, 0 °C, 94%; (k) Zn, NH_4OAc aq, rt; (l) Et_2NH, CH_3CN, rt; (m) EDCI·HCl, HOAt, CH_2Cl_2-DMF, rt, 73% in 3 steps; (n) $AgNO_3$, 2,6-lutidine, THF-H_2O, 65 °C, 85%. PyBOP = (benzotriazole-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate.

Table 1
Cytotoxicity against HeLa S_3 cells of aurilide and the artificial analogs

Compound	Cytotoxicity IC_{50} (ng/mL)
1	2.4–11
2	>4000
3	17
4	20
5	260
6	32
7	420
8	140
9	>10,000

studies on biological activity of aurilide are currently in progress.

Acknowledgments

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6. Satisfactory spectroscopic data were obtained for synthetic analogs.
Compound **3**: $[\alpha]_D^{24}$ + 6.0 (*c* 0.05, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ7.45 (d, *J* = 9.4 Hz, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 6.78 (d, *J* = 8.7 Hz, 1H), 5.44 (dd, *J* = 7.3, 7.3 Hz, 1H), 5.21 (t, *J* = 7.3 Hz, 1H), 4.95 (d, *J* = 4.5 Hz, 1H), 4.94 (d, *J* = 4.5 Hz, 1H), 4.88 (dd, *J* = 6.4, 9.4 Hz, 1H), 4.71 (dd, *J* = 8.7, 7.9 Hz, 1H), 4.28 (q, *J* = 7.2 Hz, 1H), 4.05 (d, *J* = 17.7 Hz, 1H), 3.32 (d, *J* = 17.7 Hz, 1H), 3.19 (s, 2.6H), 3.13 (s, 0.4H), 3.01 (s, 2.6H), 2.92 (s, 2.6H) 2.86 (s, 0.4 H), 2.76 (s, 0.4 H), 2.17 (m, 2H), 2.14–1.21 (m, 13H), 1.89 (s, 3H), 1.54 (s, 3H), 1.45 (d, *J* = 7.2 Hz, 3H), 0.99–0.76 (m, 27H), 0.76 (d, *J* = 7.0 Hz, 2.6H), 0.66 (d, *J* = 7.0 Hz, 0.4H); IR ($CHCl_3$) 3318, 1733, 1684, 1652, 1261, 1097, 804 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{44}H_{75}N_5NaO_9$ $(M+Na)^+$ 840.5463, found 840.5454.
Compound **4**: $[\alpha]_D^{26}$ + 2.8 (*c* 0.32, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ7.45 (d, *J* = 8.9 Hz, 1H), 7.20 (m, 1H), 6.91 (m, 1H), 6.89. (d, *J* = 8.6 Hz, 1H), 5.51 (dd, *J* = 6.8, 6.8 Hz, 1H), 5.31 (t, *J* = 7.0 Hz, 0.3H), 5.19 (t, *J* = 7.0 Hz, 0.7H), 5.01 (d, *J* = 10.5 Hz, 1H), 4.96 (m, 1H), 4.87 (d, *J* = 5.4 Hz, 1H), 4.65 (dd, *J* = 8.9, 8.9 Hz, 1H), 4.51 (m, 1H), 4.03 (d, *J* = 17.8 Hz, 1H), 3.77–3.69 (m, 2H), 3.53 (d, *J* = 17.8 Hz, 1H), 3.24 (s, 2.3H), 3.19 (s, 0.7H), 3.12–2.99 (m, 2H), 2.99 (s, 2.6H), 2.94 (s, 2.6H), 2.76 (s, 0.4H), 2.63 (s, 0.4H), 2.24–1.98 (m, 10H), 1.90 (s, 3H), 1.81–1.26 (m, 12H), 1.56 (s, 3H), 1.43 (s, 9H),1.08–0.79 (m, 24H), 0.76 (d, *J* = 7.3 Hz, 3H); IR ($CHCl_3$)

3342, 1684, 1653, 1457, 1251, 754 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{52}H_{90}N_6NaO_{12}$ $(M+Na)^+$ 1013.6514, found 1013.6506.

Compound **5**: $[\alpha]_D^{21}$ +2.6 (*c* 0.43, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 9.63 (d, *J* = 7.6 Hz, 1H), 8.03 (d, *J* = 9.2 Hz, 1H), 7.34 (m, 1H), 5.51 (t, *J* = 8.6 Hz, 1H), 5.18 (m, 1H), 5.09 (dd, *J* = 7.0, 7.0 Hz, 1H), 4.99 (d, *J* = 11.1 Hz, 1H), 4.83 (d,*J* = 4.6 Hz, 1H), 4.32 (dd, *J* = 7.8, 7.8 Hz, 1H), 3.95 (d, *J* = 18.1 Hz, 1H), 3.79 (m, 1H), 3.46 (q, *J* = 7.0 Hz, 1H), 3.38 (d, *J* = 18.1Hz, 1H), 3.28 (m, 1H), 3.27 (s, 3H), 3.05 (s, 3H), 2.88 (s, 3H), 2.84 (m, 1H), 2.22–1.86 (m, 8H), 1.93 (s, 3H), 1.73–1.22 (m, 10H), 1.53 (s, 3H), 1.46 (s, 9H), 1.43 (d, *J* = 7.0 Hz, 3H), 1.04–0.87 (m, 21H), 0.72 (d, *J* = 6.8 Hz, 3H); IR ($CHCl_3$) 3290 (br), 1683, 1652, 1252, 1092, 755 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{50}H_{86}N_6NaO_{12}$ $(M+Na)^+$ 985.6201, found 985.6195.

Compound **6**: $[\alpha]_D^{24}$ − 13.8 (*c* 0.32, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.38 (d, *J* = 9.2 Hz, 1H), 7.23 (dd, *J* = 5.5, 9.2 Hz, 1H), 7.19 (m, 0.8H), 7.01 (m, 0.2H), 6.72 (d, *J* = 8.6 Hz, 0.8H), 6.59 (d, *J* = 9.6 Hz, 0.2H), 5.33 (dd, *J* = 7.2, 7.2 Hz, 0.2H), 5.50 (dd, *J* = 7.1, 7.1 Hz, 0.8H), 5.33 (t, *J* = 7.7 Hz, 0.2H), 5.14 (t, *J* = 7.3 Hz, 0.8H), 5.09 (d, *J* = 12.0 Hz, 0.2H), 4.99 (d, *J* = 11.1 Hz, 0.8H), 4.91 (dd, *J* = 6.0, 9.2 Hz, 1H), 4.85 (m, 0.8H), 4.79 (d, *J* = 5.4 Hz, 1H), 4.73 (m, 0.2H), 4.65 (m, 0.3H), 4.59 (m, 0.7H), 4.05 (d, *J* = 17.7 Hz, 1H), 3.81 (dt, *J* = 7.1, 7.1 Hz, 1H), 3.81 (m, 1H), 3.48 (d, *J* = 17.7 Hz, 1H), 3.23 (s, 2.6H), 3.22 (s, 0.4H), 3.14–3.04 (m, 2H), 2 96 (s, 0.4H), 2.94 (s, 2.6H), 2.92 (s, 2.6H), 2.91 (s, 0.4H), 2.22 (m, 1H), 2.17–1.96 (m, 5H), 1.89 (s, 2.6H), 1.77 (s, 0.4H), 1.69–1.58 (m, 2H), 1.64 (s, 0.4H), 1.58–1.24 (m, 10H), 1.55 (s, 2.6H), 1.43 (d, *J* = 7.8 Hz, 3H), 1.42 (s, 9H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.99–0.82 (m, 18H), 0.75 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 172.0, 171.7, 170.2, 170.0, 169.9, 168.8, 168.6, 156.0, 144.0, 134.2, 130.3, 128.3, 82.5, 77.5, 71.2, 58.5, 54.2, 53.9, 51.8, 51.2, 48.9, 40.3, 40.1, 38.0, 37.0, 36.5, 36.5, 31.8, 31.7, 30.7, 30.3, 29.5, 28.6, 28.6, 28.6, 26.0, 24.8, 23.2, 23.0, 22.8, 21.1, 19.7, 17.7, 14.6, 14.0, 13.8, 12.7, 11.8, 11.0, 10.3; IR ($CHCl_3$) 3330 (br), 1693, 1682, 1651, 1633, 1537, 1489, 1415, 1250, 1093, 1041, 955 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{50}H_{86}N_6O_{12}Na$ $(M+Na)^+$ 985.6201, found 985.6206.

Compound **7**: ^1H NMR (270 MHz, $CDCl_3$) δ 7.76 (d, *J* = 7.3 Hz, 2H), 7.59 (d, *J* = 7.3 Hz, 2H), 7.20–7.42 (m, 4H), 7.17 (d, *J* = 6.0, 1H), 7.08 (m, 1H), 6.73 (d, *J* = 6.5 Hz,1H), 5.51 (dd, *J* = 6.8, 6.8 Hz, 1H), 5.36 (br d, *J* = 9.2 Hz, 1H), 5.24 (d, *J* = 7.0 Hz, 1H), 5.12 (br t, *J* = 5.7 Hz, 1H), 4.99–4.92 (m, 3H), 4.82 (dd, *J* = 6.4, 8.9 Hz, 1H), 4.53 (q, *J* = 7.3 Hz, 1H), 4.38 (d, *J* = 7.0 Hz, 1H), 4.38 (d, *J* = 7.0 Hz, 1H), 4.23 (br t, *J* = 5.7 Hz, 1H), 4.07 (d, *J* = 17.3 Hz, 1H), 3.47 (d, *J* = 17.3 Hz, 1H), 3.18–3.10 (m, 2H), 3.12 (s, 3H), 3.00 (s, 3H), 2.96 (s, 3H), 2.51 (m, 1H), 2.37–1.78 (m, 10H), 2.32 (t, *J* = 7.3 Hz, 2H), 1.90 (s, 3H), 1.82 (s, 3H), 1.23–1.65 (m, 8H), 1.40 (d, *J* = 7.3 Hz, 3H), 1.02–0.86 (m, 27H), 0.82 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 172.3, 171.82, 171.77, 171.4, 170.0, 169.6, 168.2, 167.6, 156.4, 144.0, 141.8, 141.3, 139.9, 134.3, 130.1, 128.5, 127.7, 127.0, 103.7, 81.8, 77.4, 72.5, 66.6, 54.7, 54.1, 53.5, 52.1, 51.5, 47.5, 40.1, 37.9, 37.6, 37.2, 36.1, 34.5, 32.8, 31.3, 31.2, 30.5, 29.8, 27.8, 26.3, 26.2, 24.8, 23.3, 22.7, 21.1, 20.1, 19.8, 17.5, 16.8, 14.4, 14.28, 14.25, 14.0, 12.8, 11.9, 11.0, 10.4 IR ($CHCl_3$) 3348, 3298, 1717, 1684, 1635, 1217, 1095, 756 cm^{-1}.

Compound **8**: $[\alpha]_D^{25}$ +14.8 (*c* 0.87, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.28 (m, 1H), 7.21 (d, *J* = 9.2 Hz, 1H), 7.06 (dd, *J* = 5.1, 8.4 Hz, 1H), 6.72 (t, *J* = 5.7 Hz, 1H), 5.47 (d, *J* = 6.8 Hz, 1H), 5.22 (t, *J* = 7.3 Hz, 1H), 5.22 (m, 1H), 5.04 (d, *J* = 10.3 Hz, 1H), 4.96 (dd, *J* = 5.1, 9.2 Hz, 1H), 4.78 (d, *J* = 4.3 Hz, 1H), 4.65 (m, 1H), 4.17 (m, 1H), 4.12 (d, *J* = 17.7 Hz, 1H), 3.44 (d, *J* = 17.7 Hz, 1H), 3.23–3.09 (m, 2H), 3.18 (s, 3H), 3.00 (s, 3 H), 2 92 (s, 3H), 2.74–2.61 (m, 2H), 2.57–2.41 (m, 2H), 2.37–2.17 (m, 2H), 2.22 (t, *J* = 7.0 Hz, 2H), 2.12–1.90 (m, 5H), 1.87 (s, 3H), 1.69 (m, 1H), 1.54–1.39 (m, 7H), 1.54 (s, 3H), 1.40 (d, *J* = 7.3 Hz, 3H), 1.34–1.09 (m, 4H), 1.00–0.75 (m, 24H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.76 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.0, 172.6, 172.5, 172.3, 171.8, 171.0, 170.5, 169.8, 168.3, 167.9, 141.5, 134.3, 130.0, 128.6, 81.2, 77.4, 72.8, 56.5, 54.3, 54.3, 52.0, 51.5, 39.5, 38.0, 37.6, 37.6, 36.2, 34.6, 34.4, 31.5, 31.2, 31.1, 30.7, 30.6, 29.1, 28.0, 26.3, 26.1, 24.8, 24.7, 23.2, 22.8, 21.1, 20.0, 19.7, 18.2, 17.2, 14.6, 14.1, 14.0, 12.8, 11.9, 11.5, 10.5; IR ($CHCl_3$) 3346 (br), 1732, 1682, 1651, 1539, 1456, 1415, 1217, 1097, 955 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{54}H_{90}N_6O_{14}Na$ $(M+Na)^+$ 1069.6413, found 1069.6407.

Compound **9**:$[\alpha]_D^{25}$ + 10.1 (*c* 1.49, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.1 Hz, 0.4H), 7.08 (d, *J* = 8.9 Hz, 0.6H),6.90 (d, *J* = 8.9 Hz, 0.4H), 6.87 (m, 1H), 6.69 (d, *J* = 8.1 Hz, 0.6H), 6.62 (t, *J* = 6.2 Hz, 0.4H), 6.38 (t, *J* = 5.5 Hz, 0.6H), 5.54–5.40 (m, 2H), 5.27 (d, *J* = 2.7 Hz, 0.6H), 5.25 (m, 0.6H), 5.16–5.05 (m, 2.8H), 4.93–4.75 (m, 1.4H), 4.69 (d, *J* = 5.9 Hz, 0.6H), 4.57 (d, *J* = 16.6 Hz, 0.6H), 4.44 (d, *J* = 16.1 Hz, 0.4H), 3.75 (d, *J* = 16.1 Hz, 0.4H), 3.45 (d, *J* = 16.6 Hz, 0.6H), 3.31–3.03 (m, 2H), 3.10 (s, 1.8H), 3.09 (s, 1.2H), 3.03, (s, 1.2H), 2.95 (s, 1.8H), 2.88 (s, 1.8H), 2.81 (s, 1.2H), 2.70–2.66 (m, 2H), 2.62–2.48 (m, 2H), 2.41 (m, 1H), 2.35–2.22 (m, 3H), 2.17–1.91 (m, 5H), 1.87 (s, 1.8H), 1.78 (s, 1.2H), 1.72–1.21 (m, 12H), 1.60 (s, 3H), 1.41 (d, *J* = 7.3 Hz, 3H), 0.99–0.81 (m, 24H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.77 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 175.7, 174.9, 172.9, 172.7, 172.6, 172.5, 172.2, 171.6, 171.1, 171.0, 170.7, 170.5, 170.4, 170.2, 169.2, 168.4, 167.3, 166.9, 166.6, 140.1, 134.4, 130.3, 130.0, 129.2, 129.0, 81.9, 81.0, 76.2, 73.0, 72.5, 55.1, 54.5, 54.3, 53.5, 52.8, 52.5, 52.2, 51.1, 50.7, 39.5, 39.4, 38.1, 38.0, 37.6, 37.0, 35.7, 34.7, 34.3, 32.0, 31.9, 31.8, 31.5, 31.3, 31.2, 30.9, 30.7, 30.4, 29.1, 26.3, 26.3, 26.1, 25.7, 24.9, 24.8, 24.5, 23.4, 23.3, 22.7, 22.5, 21.1, 21.0, 20.1, 20.0, 19.8, 19.5, 18.8, 17.6, 17.1, 16.8, 15.3, 14.9, 14.7, 14.2, 14.0, 13.9, 12.8, 12.5, 12.0, 11.7, 11.5, 11.0, 10.6; IR ($CHCl_3$) 3354 (br), 1732, 1682, 1651, 1539, 1464, 1415, 1217, 1093, 955 cm^{-1}; MS (ESI) *m*/*z* calcd for $C_{54}H_{90}N_6O_{14}Na$ $(M+Na)^+$ 1069.6413, found 1069.6416.

7. Coste, J.; Le-Nguyen, D.; Castro, B. *Tetrahedron Lett.* **1990**, *31*, 205.
8. Conditions: $FmocNH(CH_2)_5CO_2H$, EDCI·HCl, DMAP, CH_2Cl_2, rt, 83%.
9. Conditions: (i) Et_2NH, CH_3CN, rt; (ii) succinic anhydride, CH_2Cl_2, rt, 78% in 2 steps.