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DESIGN AND SYNTHESIS OF TELOMESTATIN DERIVATIVES AND THEIR INHIBITORY ACTIVITY OF TELOMERASE

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Abstract – Telomestatin derivatives of **2a**-**2c**, which have macrocyclic bisamide structure, were designed and synthesized. One of these compounds (**2a)** showed inhibitory activity of telomerase with an IC_{50} of 2 μM.

Telomestatin (**1**) is a natural product isolated from *Streptomyces anulatus* 3533-SV4 by the screening of Telomeric Repeat Amplification Protocol (TRAP) assay.[1] Telomestatin (**1**) shows potent telomerase inhibitory activity with an IC_{50} of 5 nM, and it also has been realized to stabilize strongly the telomeric G-quadruplex formation.[2] Thus, telomestatin (**1**) appears to be an ideal lead compound for the telomere-targeted anticancer agent.[3,4] Telomestatin (**1**) is also used as a tool for studying biological

effects inducing the formation of G-quadruplex structure in cells.[2] Herein, we described the synthesis of macrocyclic bisamide compounds (**2a-c**),[4] which is designed as a new synthetically practical telomerase inhibitor, and evaluation of their telomerase inhibitory activity.

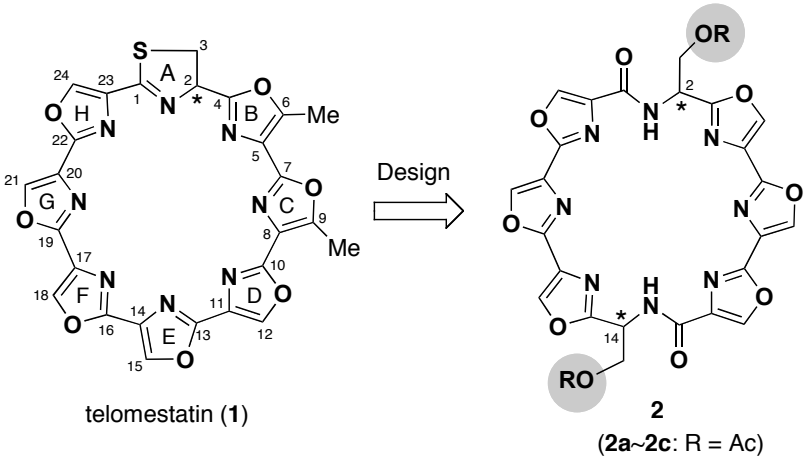
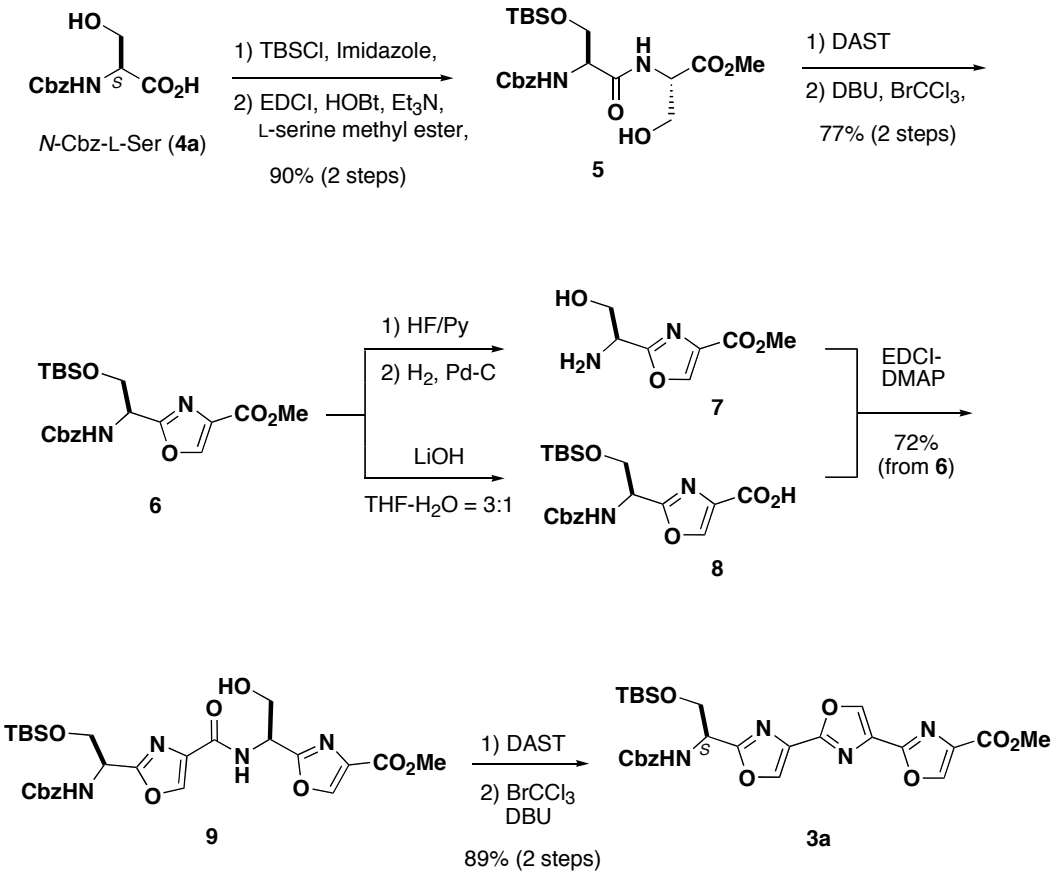


Figure 1. Design of Telomestatin Derivative (**2**).

Telomestatin (**1**) has a characteristic macrocyclic ring system, which consists of sequential pentaoxazoles, bismethyloxazoles, and a thiazoline. These structural features of **1** are suggested to bind to G-quartet strongly by overlapping, and this interaction is believed to promote the formation and stabilization of G-quadruplex structure.[2] To increase this interaction by using the designed telomestatin derivative, installation of additional functional groups, such as carbonyl, hydroxyl, and/or amino groups, together with macrocyclic ring system to **1** would be required. Based upon this concept, we designed macrocyclic bisamide (**2**) as a synthetic derivative of **1**. This derivative has two hydroxyl groups (R = H), and variety of functional groups can be introduced to this moiety. Since the chiral centers at C2 and C14 in (**2**) are expected to affect the binding to G-quartet, we synthesized three possible diastereomers of **2**, i.e., **2a**-**2c**.[5,6]

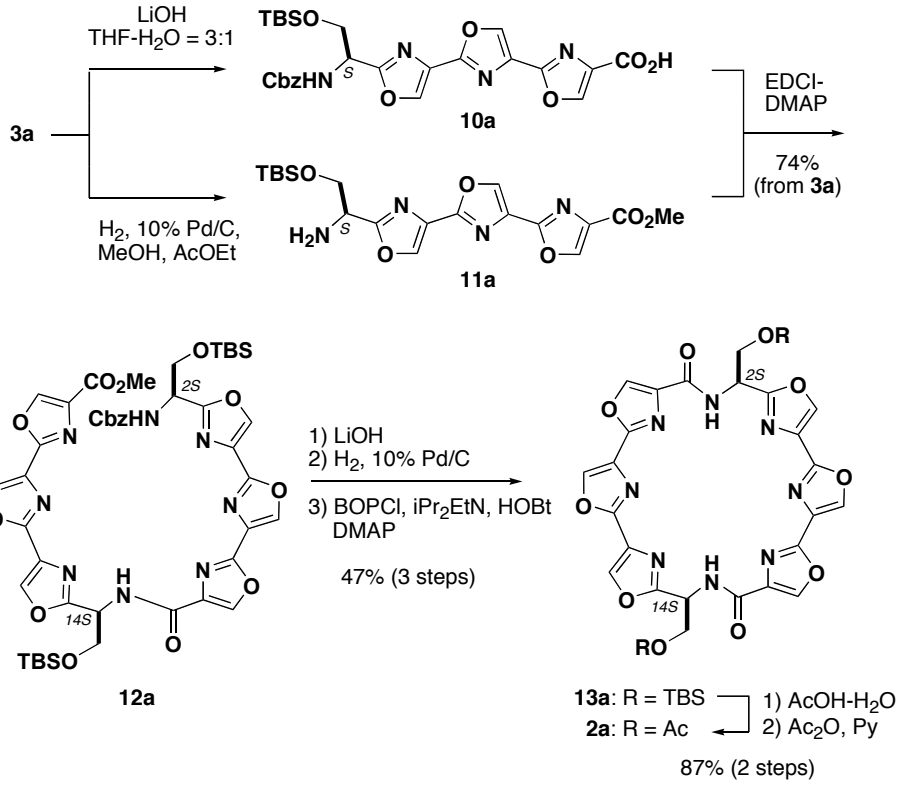
Trioxazole (**3a)** was synthesized from *N*-Cbz-L-serine (**4a**) (Scheme 1). Hydroxyl group of **4a** was protected with TBS ether and resulting carboxylic acid was reacted with L-serine methyl ester in the presence of 1-[3-(diethylamino)propyl]-3-ethylcarbodiimide hydrochloride (EDCI), 1-hydroxybenzotriazole (HOBt) and triethylamine to give amide (**5**) in 90% yield. Reaction of **5** with diethylaminosulfurtrifluoride (DAST) in CH_2Cl_2 at 0 ºC gave oxazoline,[7] which was subsequent treatment with bromotrichloromethane in the presence of DBU to give oxazole (**6**) in 77% yield from **5**.[8] Deprotection of the TBS and Cbz groups of **6** gave aminoalcohol (**7**). At the same time, methyl ester of **6** was hydrolyzed with lithium hydroxide to give carboxylic acid (**8**). These two segments, (**7**) and (**8**), were coupled in the presence of EDCI and DMAP to give amide (**9**) in 72% from **6**.

Hydroxylmethylamide moiety of **9** was converted into oxazole with DAST and subsequent reaction with bromotrichloromethane and DBU to give trioxazole (**3a**) in 89%.

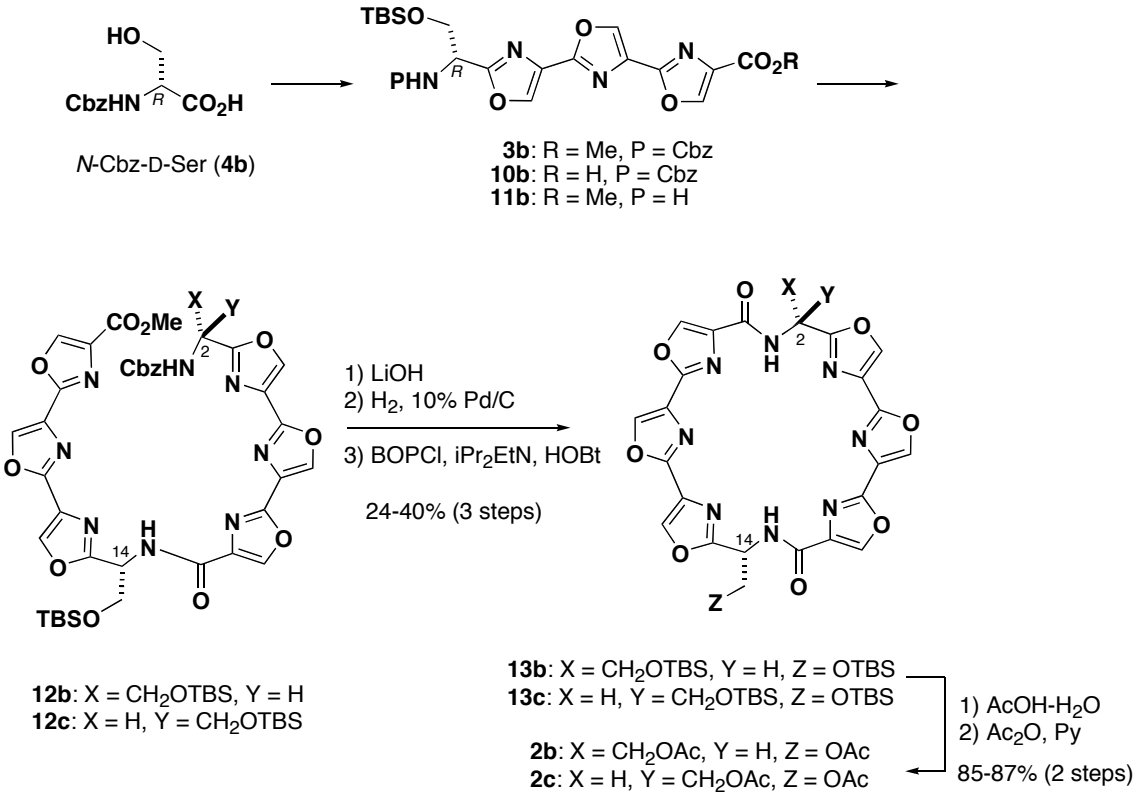


Scheme 1. Synthesis of Trioxazole (**3a**).

Macrocyclic bisamide [(*2S,14S*)-**2a**] was synthesized from the trioxazole (**3a**) (Scheme 2). Methyl ester and Cbz groups of **3a** was removed to give carboxylic acid (**10a**) and amine (**11a**), respectively. These two segments were reacted with EDCI in the presence of HOBt and triethylamine to give linear bis-trioxazole (**12a**). After hydrolysis of ester group and deprotection of Cbz group of **12a**, resulting amino acid was subjected to the macrocyclization reaction using *N,N*-bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) and diisopropylethylamine under the high dilution condition (1 mM) in dichloromethane-DMF to give macrocyclic bisamide (**13a**) in 47% yield from **12a**. The TBS ether was exchanged to acetate to give bisamide acetate [(*2S,14S*)-**2a**] in 87% yield.



Scheme 2. Synthesis of Bistrioxazole Acetate (**2a**).



Scheme 3. Synthesis of Bistrioxazole Acetate (**2b**) and (**2c**).

The macrocyclic bisamide acetate [(*2R*,*14R*)-**2b**] was synthesized from *N*-Cbz-D-serine (**4b**) by the same way as **2a** via **3b** and **12b** (Scheme 3). Meso bisamide acetate (**2c**) was also synthesized from carboxylic acid (**10b**) and amine (**11a**). These two segments were efficiently converted into **2c** via **12c** (Scheme 3).

Designed macrocyclic bisamide compounds (**2a**-**2c**) in hand, telomerase inhibitory activity of these derivatives were evaluated by TRAP assay. Among them, **2a**, which was derived from *N*-Cbz-L-serine (**4a**), showed telomerase inhibitory activity with an IC_{50} of 2 μM[9]. On the other hand, **2b** and **2c** did not show inhibitory activity at the concentration of 10 μM.

In conclusion, we have designed and synthesized macrocyclic bisamide type telomestatin derivatives (**2a**-**2c**). Biological activity of these derivatives was examined, and we found that the only **2a** showed telomerase inhibitory activity with an IC_{50} of 2 μM. These results suggest that the asymmetric centers in derivatives (**2**) importantly affect the interaction with G-quartet. Additional structural development focusing on functional group at hydroxylmethyl moiety in **2a** are in progress.

EXPERIMENTAL

General: Flash chromatography was performed using Silica gel 60 (spherical, particle size 0.040-0.100 mm; Kanto Co., Inc., Japan). Optical rotations were measured with a JASCO DIP polarimeter 370. ^{1}H and ^{13}C NMR spectra were recorded on JEOL EX300, ECA/ECX400 instruments. Mass spectra were recorded on JEOL JMS-T100LC spectrometer.

Oxazole (**6**): To a solution of **5** (34.2 g, 75.4 mmol) in CH_2Cl_2 (100 mL) was added DAST (13 mL, 98.0 mmol) at 0 °C under N_2, and the mixture was stirred for 10 min. To the reaction mixture was added sat-$NaHCO_3$, and the organic layer was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (75 mL). To the solution was added DBU (24 mL, 147.2 mmol) and $BrCCl_3$ (14.6 mL, 147.2 mmol) at 0 °C under N_2, and the mixture was stirred at rt for 1.5 h. H_2O was added to the reaction mixture at 0 °C, and organic layer was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel (hexane-AcOEt = 8:1) to give oxazole (**6**) as a pale yellow oil (24.7 g, 77%). $[\alpha]^{25}_D$ = -7.4 (*c* 2.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.36 (m, 5H), 5.77-5.75 (d, *J* = 8.3 Hz, 1H), 5.17-5.07 (m, 3H), 4.11-4.07 (dd, *J* = 3.7, 11.7 Hz, 1H), 3.96-3.92 (m, 4H), 0.79 (s, 9H), -0.03 (s, 3H). –0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.2, 161.2, 155.6, 144.0, 135.9, 133.2, 128.3, 128.0, 128.0, 67.0, 64.1, 52.1, 51.3, 25.4, 17.9, -5.8; HRMS (ESI, M+Na) calcd for $C_{21}H_{30}N_2O_6SiNa$ 457.1771, found 457.1758.

Amide (**9**): To a solution of oxazole (**6**) (122 mg, 0.281 mmol) in THF (2 mL) in a polypropylene tube, was added HF-pyridine complex (0.1 mL) at 0 ºC. After stirring at rt for 10 h, sat- $NaHCO_3$ and solid

$NaHCO_3$ was added. The mixture was dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (hexane-AcOEt = 1:4) to afford alcohol (91 mg, 99%) as a clear oil. To a solution of the alcohol in MeOH (5 mL) was added 10% Pd/C and the reaction mixture was stirred at rt under an atmosphere of hydrogen gas (balloon). After 8 h, the reaction mixture was filtered through a pad of Celite and eluted with MeOH. The solution was concentrated *in vacuo* to give aminoalcohol (**7**) (40 mg), whcih was used without further purification. To a solution of oxazole (**6**) (116 mg, 0.266 mmol) in THF-H_2O (3:1, 2.6 mL), was added LiOH (13 mg, 0.532 mmol) at 0 ºC. After stirring at rt for 1 h, Dowex® 50WX4 ion-exchange resign was added. The reaction mixture was filtered through a cotton with MeOH and the filtrates were concentrated *in vacuo* to give carboxylic acid (**8**) (110 mg), which was used without further purification. To a solution of aminoalcohol (**7**) and carboxylic acid (**8**) in DMF (5 mL) was added DMAP (65 mg, 0.532 mmol) and EDCI (102 mg, 0.532 mmol) at rt. After stirring for 18 h, H_2O was added to the reaction mixture, and the mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified on silica gel ($CHCl_3$- AcOEt = 1:3) to give amide (**9**) (113 mg, 72%, 3 steps) as a colorless oil. $[\alpha]^{25}_D$ = -19.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.19 (s, 1H), 8.12 (s, 1H), 7.91-7.88 (d, *J* = 8.6 Hz, 1H), 7.36 (m, 5H), 5.86-5.83 (d, *J* = 8.6 Hz, 1H), 5.51-5.45 (dt, *J* = 4.2, 8.6 Hz, 1H), 5.18-5.09 (m, 2H), 5.03-4.98 (dt, *J* = 3.7, 8.6 Hz, 1H), 4.27-4.24 (m, 1H), 4.05-3.89 (m, 6H), 0.788 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.7, 162.4, 161.3, 160.4, 155.8, 144.4, 141.8, 136.0, 135.4, 133.1, 128.5, 128.2, 67.3, 63.9, 63.0, 52.1, 51.2, 48.6, 25.5, 18.1, -5.7; HRMS (ESI, M+Na) calcd for $C_{27}H_{36}N_4O_9SiNa$ 611.2149, found 611.2147.

Trioxazole (**3a**): To a solution of amide (**9**) (550 mg, 0.935 mmol) in CH_2Cl_2 (10 mL) was added DAST (136 μL, 1.03 mmol) at 0 °C under N_2, and the mixture was stirred for 10 min. To the reaction mixture was added sat-$NaHCO_3$, and organic layer was extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was dissolved with CH_2Cl_2 (9.5 mL), and to the resulting solution was added DBU (0.38 mL, 2.34 mmol) and $BrCCl_3$ (0.23 mL, 2.34 mmol) at 0 °C, and the mixture was stirred for 4 h at rt. The reaction mixture was cooled at 0 °C, and H_2O was added. The organic layer was extracted with CH_2Cl_2, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was chromatographed on silica gel (hexane-AcOEt = 1:1) to give oxazole (**3a)** as a pale yellow powder (403 mg, 77%, 2 steps). $[\alpha]^{25}_D$ = -11.2 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.32 (s, 2H), 7.36 (m, 5H), 5.81-5.79 (d, *J* = 8.8 Hz, 1H), 5.19-5.10 (m, 3H), 4.15-4.10 (d, *J* = 3.7, 10.1 Hz 1H), 4.00-3.98 (br, 1H), 3.97-3.95 (m, 4H), 0.78 (s, 9H), -0.03 (s, 3H), -0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 161.3, 156.0, 155.8, 155.4, 143.9, 143.8, 139.6, 139.4, 139.3, 136.0, 134.3, 130.8, 129.9, 128.5, 128.2, 67.3, 64.3, 52.4, 51.5, 25.5, 18.1, -5.6; HRMS (ESI, M+Na) calcd for $C_{27}H_{32}N_4O_8SiNa$ 591.1887, found 591.1886.

Bis-trioxazole (**12a**): To a solution of trioxazole (**3a**) (119 mg, 0.210 mmol) in MeOH-AcOEt (1:1, 8 mL) was added 10% Pd/C and the reaction mixture was stirred at rt under an atmosphere of hydrogen gas (balloon). After 3 h, the reaction mixture was filtered through a pad of Celite and eluted with MeOH. The solution was concentrated *in vacuo* to give amine (**11a**), which was used without further purification. To a solution of trioxazole (**3a**) (119 mg, 0.211 mmol) in THF-H_2O = 3:1 (3 mL), was added LiOH (17.7 mg, 0.422 mmol) at 0 ºC. After stirring at rt for 45 min, Dowex® 50WX4 ion-exchange resign was added. The reaction mixture was filtered through a cotton with MeOH, and the filtrates were concentrated *in vacuo* to give carboxylic acid (**10a**), which was used without further purification. To a solution of amine (**11a**) and carboxylic acid (**10a**) in DMF (4 mL) was added EDCI (81 mg, 0.420 mmol), HOBt (29 mg, 0.210 mmol) and Et_3N (59 μL, 0.420 mmol), and the mixture was stirred at rt. After stirring for 24 h, the reaction was quenched with H_2O and the reaction mixture was extracted with AcOEt. The organic layer was washed with H_2O and brine, dried over $MgSO_4$, and concentrated *in vacuo*. The resulting residue was purified on silica gel ($CHCl_3$- AcOEt = 4:1) to give bis-trioxazole (**12a**) (152 mg, 0.156 mmol, 74%, 3 steps). $[\alpha]^{25}_D$ = +5.5 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.40 (s, 1H), 8.31-8.26 (m, 5H), 7.85-7.82 (d, *J* = 8.8 Hz, 1H) 7.32 (m, 5H), 5.85-5.82 (d, *J* = 8.8 Hz, 1H), 5.53-5.49 (dt, *J* = 4.6, 8.5 Hz, 1H), 5.16-5.06 (m, 3H), 4.22-4.18 (dd, *J* = 4.4, 10.1 Hz, 1H), 4.11-4.03 (m, 2H), 3.98-3.90 (m, 4H), 0.81 (s, 9H), 0.75 (s, 9H), 0.00 (s, 3H), -0.03 (s, 3H), -0.06 (s, 3H), -0.09 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.9, 163.3, 161.1, 159.8, 156.0, 155.9, 155.7, 155.3, 154.4, 143.8, 141.5, 139.6, 139.3, 139.0, 136.6, 135.9, 134.2, 130.8, 130.6, 129.9, 129.8, 128.4, 128.0, 67.1, 64.2, 64.0, 52.3, 51.8, 49.1, 25.5, 18.0, -5.7; HRMS (ESI, M+Na) calcd for $C_{45}H_{54}N_8O_{13}Si_2Na$ 993.3246, found 993.3213

Macrocyclic bisamide (**13a**): A mixture of bis-trioxazole (**12a**) (151 mg, 0.156 mmol) and lithium hydroxide (16 mg, 0.390 mmol) in THF-H_2O (3:1, 6 mL) was stirred at rt for 1.5 h. To the reaction mixture was added Dowex® 50WX4 ion-exchange resign. The reaction mixture was filtered through a cotton with MeOH, and the filtrates were concentrated *in vacuo* to give carboxylic acid. The residue was dissolved in MeOH-AcOEt solution (1:1, 20 mL), and 10% Pd/C was added. The mixture was stirred at rt under hydrogen (balloon) for 20 h. The reaction mixture was filtered through a pad of Celite and the filtrates were concentrated *in vacuo*. To a solution of the residue in DMF-CH_2Cl_2 (1:2, 156 mL) was added DMAP (381 mg, 1.56 mmol), HOBt (211 mg, 1.56 mmol), diisopropylethylamine (265 μL, 1.56 mmol), and BOPCl (397 mg, 1.56 mmol). The resulting mixture was stirred for another 2 days. To the reaction mixture was added H_2O and the organic layer was extracted with AcOEt. The extracts were washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column ($CHCl_3$:MeOH = 50:1) to give **13a** as an oil (59 mg, 47%). $[\alpha]^{25}_D$ = +18.7 (*c* 3.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.50-8.49 (d, *J* = 7.4 Hz, 2H), 8.21-8.18 (m, 6H), 5.37-5.36 (br, 2H), 4.16-4.13 (dd, *J* = 3.6, 9.6 Hz, 2H), 3.97-3.93 (dd, *J* = 6.9, 9.6 Hz, 2H), 0.786 (s, 18H), -0.0265

(s, 6H), -0.0677 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7, 159.8, 156.0, 154.6, 140.8, 139.1, 138.4, 136.7, 130.9, 129.7, 64.6, 50.2, 25.6, 18.1, -5.64; HRMS (ESI, M+Na) calcd for $C_{36}H_{44}N_8O_{10}Si_2Na$ 827.2617, found 827.2659.

Macrocyclic bisamide acetate (**2a**): Macrocyclic bis-amide (**13a**) (17 mg, 0.0221 mmol) was dissolved in AcOH-MeOH (4:1, 2.5mL). After stirring for 40 h at rt, the mixture was concentrated *in vacuo* to give diol. To a solution of the diol in pyridine (0.5 mL) was added Ac_2O (0.5 mL) at rt for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified on silica gel ($CHCl_3$-MeOH = 50:1) to give macrocyclic bis-amide acetate (**2a**) (13 mg, 87%, 2 steps). $[\alpha]^{25}_D$ = +42.3 (*c* 0.1, $CHCl_3$-MeOH = 3:1); ^{1}H NMR (400 MHz, DMSO *d*-6) δ 9.16-9.15 (br, 4H), 8.98 (s, 2H), 8.35-8.33 (d, *J* = 5.9 Hz), 5.68 (br, 2H), 4.66-4.64 (d, *J* = 9.2 Hz, 2H), 4.50-4.47 (d, *J* = 10.1 Hz, 2H), 1.94 (s, 6H); ^{13}C NMR (100 MHz, DMSO *d*-6) δ 170.1, 161.8, 159.0, 155.5, 154.6, 142.8, 142.4, 141.3, 135.8, 129.8, 128.6, 63.1, 47.5, 20.4; HRMS (ESI, M+Na) calcd for $C_{28}H_{20}N_8O_{12}Na$ 683.1098, found 683.1148.

Trioxazole (**3b**): $[\alpha]^{25}_D$ = +9.9 (*c* 0.8, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.43 (s, 1H), 8.32 (s, 2H), 7.36 (m, 5H), 5.79-5.76 (d, *J* = 8.4 Hz, 1H), 5.20-5.10 (m, 3H), 4.13-4.10 (m, 1H), 4.00-3.95 (m, 4H), 0.79 (s, 9H), -0.02 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 161.3, 156.0, 155.8, 155.4, 143.9, 143.8, 139.6, 139.4, 139.3, 136.0, 134.4, 130.8, 129.9, 128.5, 128.2, 67.3, 64.3, 52.5, 51.5, 25.6, 18.1, -5.7; HRMS (ESI, M+Na) calcd for $C_{27}H_{32}N_4O_8SiNa$ 591.1887, found 591.1867.

Bis-trioxazole (**12b**): $[\alpha]^{25}_D$ = -7.0 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.42 (s, 1H), 8.34-8.28 (m, 5H), 7.86-7.83 (d, *J* = 8.8 Hz, 1H), 7.37 (m, 5H), 5.80-5.77 (d, *J* = 8.4 Hz, 1H), 5.58-5.52 (dt, *J* = 4.6, 8.6 Hz, 1H), 5.20-5.10 (m, 3H), 4.26-4.21 (dd, *J* = 4.4, 10.1 Hz, 1H), 4.15-4.06 (m, 2H), 4.01-3.95 (m, 4H), 0.84 (s, 9H), 0.79 (s, 9H), 0.04 (s, 3H), 0.01 (s, 3H), -0.02 (s, 3H), -0.05 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.0, 163.4, 161.3, 159.9, 156.1, 156.0, 155.8, 155.4, 154.5, 143.9, 141.6, 139.6, 139.4, 139.1, 136.7, 136.0, 134.4, 130.9, 130.8, 130.0, 129.9, 128.5, 128.2, 67.3, 64.3, 64.1, 52.2, 51.5, 49.2, 25.6, 18.1, -5.6; HRMS (ESI, M+Na) calcd for $C_{45}H_{54}N_8O_{13}Si_2Na$ 993.3246, found 993.3216.

Macrocyclic bisamide (**13b**): $[\alpha]^{25}_D$ = -18.8 (*c* 1.5, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52-8.50 (d, *J* = 7.3 Hz, 2H), 8.22 (s, 2H), 8.19 (s, 2H), 8.18 (s, 2H), 5.40-5.35 (dd, *J* = 6.4, 11.4 Hz, 2H), 4.17-4.13 (dd, *J* = 4.1, 9.6 Hz 2H), 3.98-3.93 (dd, *J* = 6.9, 9.9 Hz 2H), 0.80 (s, 18H), -0.02 (s, 6H), -0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9 160.0 156.2 154.8 141.0 139.3, 138.5, 137.0, 131.1, 129.9, 64.6, 50.4, 25.8, 18.3, -5.4; HRMS (ESI, M+Na) calcd for $C_{36}H_{44}N_8O_{10}Si_2Na$ 827.2617, found 827.2585.

Macrocyclic bisamide acetate (**2b**): $[\alpha]^{25}_D$ = -58.1 (*c* 0.2, $CHCl_3$-MeOH = 3:1); ^{1}H NMR (400 MHz, DMSO *d*-6) δ 9.17-9.15 (br, 4H), 8.98 (s, 2H), 8.35-8.33 (d, *J* = 6.9 Hz, 2H), 5.68 (br, 2H), 4.67-4.63 (dd, *J* =3.7, 11.5 Hz, 2H), 4.50-4.46 (m 2H), 1.94 (s, 6H); ^{13}C NMR (100 MHz, DMSO *d*-6) δ 169.7, 161.7, 158.8, 155.3, 154.4, 142.3, 141.9, 140.8, 135.7, 129.6, 128.5, 63.0, 47.2, 20.1; HRMS (ESI, M+Na) calcd for $C_{28}H_{20}N_8O_{12}Na$ 683.1098, found 683.1106.

Bis-trioxazole (**12c**): $[\alpha]^{25}_{D}$ = +28.3 (*c* 2.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) I 8.41 (s, 1H), 8.33-8.29 (m, 5H), 7.85-7.82 (d, *J* = 8.7 Hz, 1H), 7.35 (m, 5H), 5.81-5.79 (d, *J* = 8.7 Hz, 1H), 5.56-5.51 (m, 1H), 5.17-5.09 (m, 3H), 4.23-4.19 (m, 1H), 4.13-4.05 (m, 2H), 3.99-3.95 (m, 1H), 3.92 (s, 3H), 0.814 (s, 9H), 0.766 (s, 9H), 0.0125 (s, 3H), -0.015 (s, 3H), -0.0414 (s, 3H), -0.0769 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 163.4, 161.2, 159.8, 156.1, 155.9, 155.8, 155.3, 154.4, 143.8, 141.5, 139.6, 139.3, 139.0, 136.6, 136.0, 134.3, 130.9, 130.7, 129.9, 129.8, 128.4, 128.2, 128.1, 67.2, 64.2, 64.0, 52.3, 51.6, 49.2, 25.5, 18.1, -5.61; HRMS (ESI, M+Na) calcd for $C_{45}H_{54}N_8O_{13}Si_2Na$ 993.3246, found 993.3229.

Macrocyclic bisamide (**13c**): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52-8.51 (d, *J* = 7.3 Hz, 2H), 8.23 (s, 2H), 8.20 (s, 2H), 8.19 (s, 2H), 5.41-5.36 (dd, *J* = 6.9, 11.5 Hz, 2H), 4.18-4.14 (dd, *J* = 4.1, 9.6 Hz, 2H), 3.98-3.94 (dd, *J* = 6.8, 10.0 Hz, 2H), 0.80 (s, 18H), -0.01 (s, 6H), -0.051 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.8, 159.9, 156.1, 154.6, 140.8, 139.1, 138.3 136.8, 130.9, 129.7, 64.4, 50.2, 25.7, 18.1, -5.59; HRMS (ESI, M+Na) calcd for $C_{36}H_{44}N_8O_{10}Si_2Na$ 827.2617, found 827.2640.

Macrocyclic bisamide acetate (**2c**): ^{1}H NMR (400 MHz, $CDCl_3$-CD_3OD = 3 : 1) δ 8.27 (s, 2H), 8.23 (s, 2H), 8.20 (s, 2H), 5.46-5.44 (dd, *J* = 3.2, 7.3 Hz, 2H), 4.50-4.46 (m, 2H), 4.38-4.34 (m, 2H), 1.83 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$-CD_3OD = 3 : 1) δ 170.7, 161.4, 160.1, 155.9, 154.6, 141.7, 140.3, 139.1, 135.9, 130.1, 129.2, 63.4, 47.3, 20.0; HRMS (ESI, M+Na) calcd for $C_{28}H_{20}N_8O_{12}Na$ 683.1098, found 683.1123.

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