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SYNTHESIS OF THE DIAZEPANONE-NUCLEOSIDE CORE STRUCTURE OF LIPOSIDOMYCINS AND CAPRAZAMYCINS BASED ON 7-*EXO* CYCLIZATION OF EPOXYAMINE

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Abstract – The diazepanone-nucleoside core structure of liposidomycins and caprazamycins has been synthesized based on 7-*exo* cyclization of epoxyamine.

Liposidomycins are a family of nucleoside antibiotics initially isolated from *Streptomyces griseosporeus* in 1985 (Figure 1).[1] Liposidomycins inhibit formation of the lipid intermediate in peptidoglycan synthesis of *Escherichia coli* at IC_{50} = 0.03 μg/mL. In particular, liposidomycin B showed anti-mycobacterial activity against *Mycobacterium phlei* IFO 3158 (MIC = 1.6 μg/mL).[1a] Caprazamycins are a family of nucleoside antibiotics initially isolated from *Streptomyces* sp. MK 730-62F2 in 2003.[2] Caprazamycin B showed anti-mycobacterial activity against drug-susceptible and multi drug-resistant *Mycobacterium tuberculosis* strains. The MICs of caprazamycin B were 3.13 μg/mL for *M. tuberculosis* H37Rv and Kurono strains, 6.25-12.5 μg/mL for drug-susceptible *M. tuberculosis*, and 6.25-12.5 μg/mL for multi drug-resistant *M. tuberculosis*.[2a] Many synthetic studies of liposidomycins and caprazamycins including syntheses of their analogues have been reported in relation to their complicated structural features and potential biological activities.[3,4] Matsuda and Ichikawa's group achieved the first total synthesis of caprazol, which represents the core structure of caprazamycins.[4a,b] Caprazol was obtained by hydrolysis of caprazamycin B in studies concerning the structural determination of caprazamycins.[2b] Furthermore, Matsuda and Ichikawa's group synthesized various caprazamycin analogues and examined their structure-activity relationship.[4c-f] In this paper, the authors wish to report the synthesis of the diazepanone-nucleoside core of liposidomycins and caprazamycins based on 7-*exo* cyclization of epoxyamine.

Dedicated to Professor Victor Snieckus on his 77th birthday

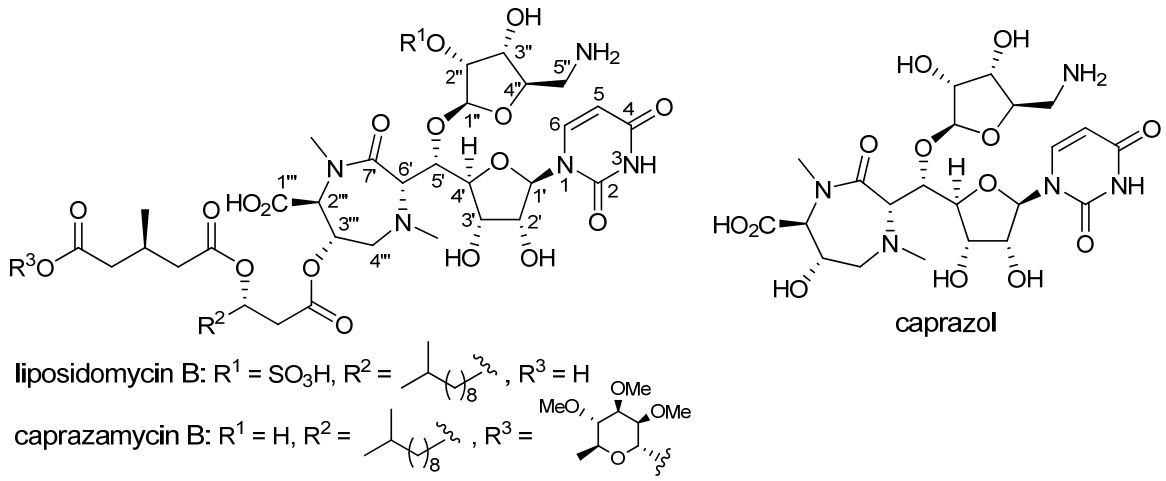
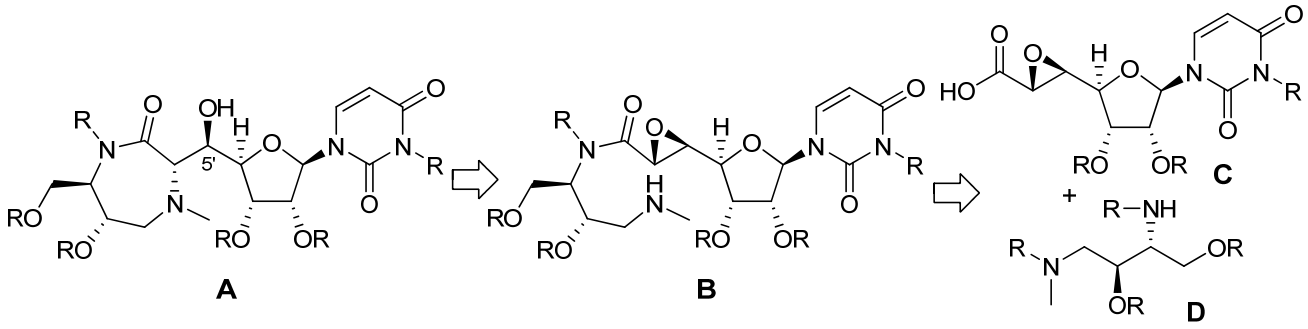


Figure 1. Structures of liposidomycin B, caprazamycin B and caprazol

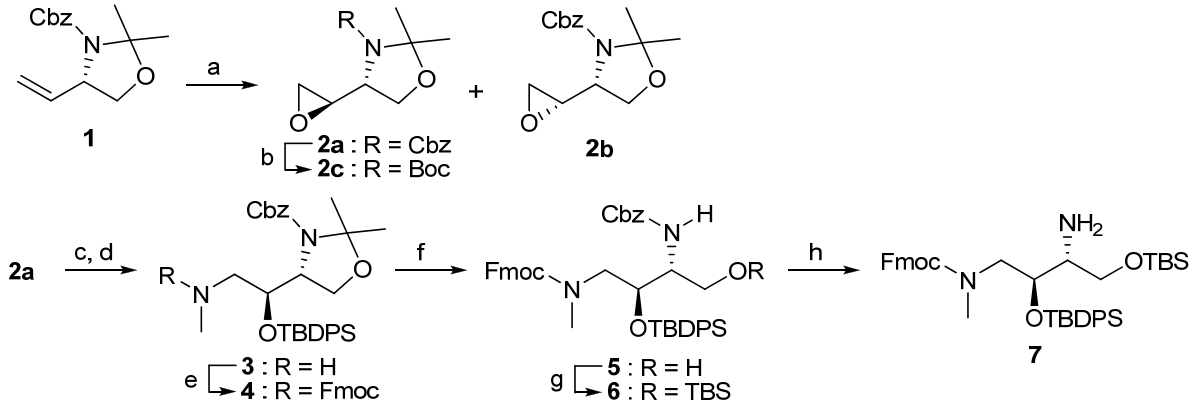
The authors planned the synthesis of 5'-*epi*-diazepanone-nucleoside core **A** of liposidomycins and caprazamycins from epoxy nucleoside **C**, which is easily prepared. Our retrosynthetic approach for diazepanone-nucleoside **A** features 7-*exo* cyclization of the epoxyamine outlined in Scheme 1. Diazepanone-nucleoside **A** is synthesized by 7-*exo* cyclization of epoxyamine **B**. Epoxyamine **B** may likely be formed through amide formation by reaction of nucleoside segment **C** and amine segment **D**. The similar synthetic study of diazepanone-nucleoside by 7-*exo* cyclization has been reported by Sarabia and co-workers.[3n,v]



Scheme 1. Synthetic strategy of the diazepanone core of liposidomycins and caprazamycins

Amine **7** corresponding to amine segment **D** in the synthetic plan was prepared from known olefin **1**[5] (Scheme 2). Epoxidation of olefin **1** with dimethyldioxirane (DMDO)[6] afforded a diastereomeric mixture of β-epoxide **2a** and α-epoxide **2b** (**2a** : **2b** = 3.4 : 1) in 93% yield. The relative configuration of β-epoxide **2a** was confirmed by chemical conversion to a known compound. β-Epoxide **2a** was treated with hydrogen in the presence of $Pd(OH)_2/C$ and di-*tert*-butyl dicarbonate (Boc_2O) to give known epoxide **2c**.[7] Opening of the epoxide in **2a** with methylamine afforded the secondary alcohol.[3d] The secondary alcohol was protected

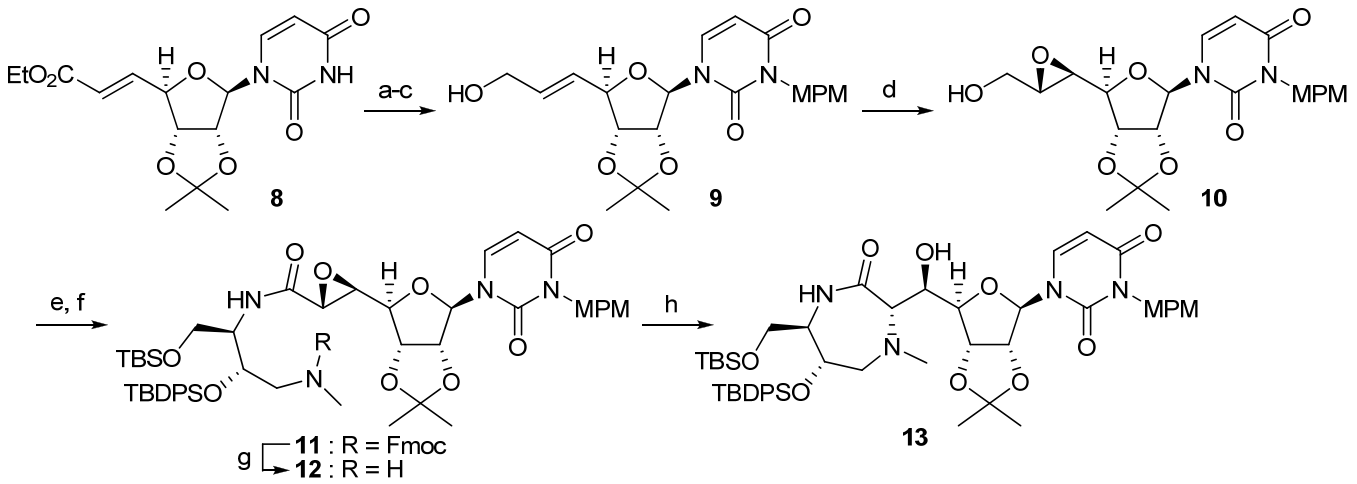
with the TBDPS group to give TBDPS ether **3** in 45% yield (2 steps). The amino group in **3** was protected with fluorenylmethyloxycarbonyl chloride (FmocCl) and 10% $NaHCO_3$ aqueous to afford Fmoc carbamate **4** in quantitative yield. The acetonide in **4** was deprotected with bismuth tribromide[8] to give alcohol **5** (62% yield) and acetonide **4** (30% recovered). The primary hydroxy group in **5** was protected with the TBS group to give TBS ether **6** in 98% yield. Deprotection of the Cbz group in **6** was accomplished by catalytic hydrogenation to give amine **7**[9] in 94% yield.



Scheme 2. *Reagents and conditions*: (a) DMDO, acetone, CH_2Cl_2, 0 °C to rt, 93%; (b) H_2, 20% $Pd(OH)_2/C$, Boc_2O, MeOH, rt, 7%, (**2a**, 46% recovered); (c) $MeNH_2$, MeOH, rt; (d) TBDPSCl, imidazole, CH_2Cl_2, rt, 45% (2 steps); (e) FmocCl, 10% $NaHCO_3$ aq., 1,4-dioxane, rt, quant.; (f) $BiBr_3$, MeCN, rt, 62%, (**4**, 30% recovered); (g) TBSCl, imidazole, DMF, rt, 98%; (h) H_2, 10% Pd/C, AcOEt, rt, 94%.

Nucleoside segment **C** in the synthetic plan was prepared from known α,β-unsaturated ester **8**.[10] α,β-Unsaturated ester **8** was reduced with DIBAH in CH_2Cl_2 at –78 °C to afford the aldehyde (Scheme 3). The aldehyde was reduced with $NaBH_4$ in MeOH to give the allylic alcohol. Direct reduction of α,β-unsaturated ester **8** to allylic alcohol with two and more equivalents of DIBAH resulted in an extremely low yield. The uracil base in the allylic alcohol was protected with MPMCl and DBU to give allylic alcohol **9** in 36% yield (3 steps). Epoxidation of allylic alcohol **9** was performed according to Sharpless' procedure to afford epoxyalcohol **10** in 87% yield. In this epoxidation, the diastereomer of **10** was not obtained.

Nucleoside segment **10** and amine segment **7** were connected by formation of an amide bond. Oxidation of epoxyalcohol **10** with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), NaClO and KBr gave the carboxylic acid.[11] Treatment of a mixture of the carboxylic acid and amine **7** with 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBt)[12] in THF afforded amide **11** in 75% yield (based on **7**). The Fmoc group of amide **11** was removed by treatment with Et_3N in THF to give epoxyamine **12** in 90% yield. Epoxyamine **12** is a precursor of the diazepanone-nucleoside. A solution of epoxyamine **12** in THF was refluxed to afford diazepanone **13** in 66% yield.



Scheme 3. *Reagents and conditions*: (a) DIBAH, CH_2Cl_2, –78 °C; (b) $NaBH_4$, MeOH, 0 °C to rt; (c) MPMCl, DBU, MeCN, rt to 60 °C, 36% (3 steps); (d) TBHP, $Ti(O^iPr)_4$, L-(+)-DIPT, 4A MS, CH_2Cl_2, –20 °C to rt, 87%; (e) TEMPO, NaClO, KBr, 5% $NaHCO_3$ aq., acetone, 0 °C to rt; (f) **7**, EDC, HOBt, THF, rt, 75% (based on **7**); (g) Et_3N, CH_2Cl_2, rt, 90%; (h) THF, reflux, 66%.

The structure of diazepanone **13** was confirmed by HMBC and NOESY spectra (Figure 2). The HMBC spectrum indicated H-5’ to be correlated with C-4’’’ and H-4’’’ to be correlated with C-7’, while Me-6’-*N* was correlated with C-7’. On the basis of these correlations, the presence of a diazepanone ring in **13** was clarified. The absolute configuration at C-6’ in **13** was determined by the following NOESY correlations: H-6’/H-3’’’, H-6’/H-4’’’ and Me-6’-*N*/H-4’’’. The structure of **13** was thus determined to be that as shown.

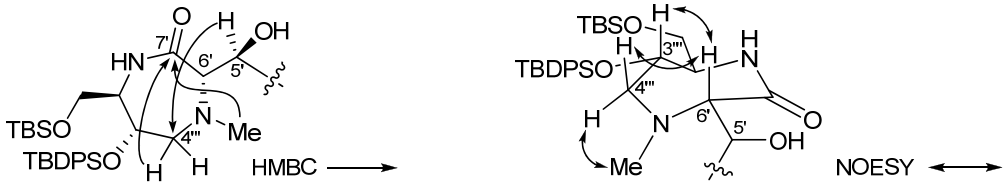


Figure 2. Selected HMBC correlations and NOE correlations of **13**

In conclusion, the authors achieved the synthesis of diazepanone-nucleoside core **13** of liposidomycins and caprazamycins based on 7-*exo* cyclization of an epoxyamine. The authors plan to invert the stereochemistry of hydroxy group at C-5’ of **13**. The synthesis of caprazamycins from diazepanone-nucleoside **13** is now being undertaken.

EXPERIMENTAL

Optical rotations were measured using a Jasco P-1030 polarimeter. Melting points (mp) were measured using a Yanako melting point apparatus MP-S3 and are uncorrected. IR spectra were recorded using a Jasco FT-IR/620 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 MHz) or

Bruker Biospin AV-600 (600 MHz) spectrometer. Chemical shifts are given on the δ (ppm) scale using tetramethylsilane (TMS) as the internal standard (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad). High resolution-electrospray ionization-mass spectra (HR-ESI-MS) were obtained using a Micromass LCT spectrometer. Elemental analysis data were obtained using an Elementar Vario EL.

(*R*)-Benzyl 2,2-dimethyl-4-((*R*)-oxiran-2-yl)oxazolidine-3-carboxylate (2a) and (*R*)-benzyl 2,2-dimethyl-4-((*S*)-oxiran-2-yl)oxazolidine-3-carboxylate (2b). To a cold (0 °C) solution of olefin **1**[5] (442 mg, 1.96 mmol) in CH_2Cl_2 (8.45 mL) was added DMDO (78.6 mL, 3.38 mmol, 0.043 M in acetone). After stirring at room temperature for 12 h, the reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 5 : 1) to give β-epoxide **2a** (339 mg, 72% yield) and α-epoxide **2b** (98.2 mg, 21% yield) as pale yellow oil, respectively. **2a**: $[\alpha]_D^{25}$ –11.1 (*c* = 1.00, $CHCl_3$); IR (neat) 2985, 1708, 1089, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.30 (5H, m), 5.22-5.10 (1.4H, m), 5.04 (0.6H, d, *J* = 12.0 Hz), 4.08 (1H, dd, *J* = 9.3, 0.9 Hz), 4.01 (1H, dd, *J* = 9.3, 5.7 Hz), 3.63 (0.4H, m), 3.48 (0.6H, m), 3.04 (0.4H, m), 2.97 (0.6H, m), 2.89 (1H, m), 2.68 (0.4H, m), 2.48 (0.6H, m), 1.68 (1.8H, s), 1.60 (1.2H, s), 1.55 (1.8H, s), 1.47 (1.2H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 152.3, 136.0, 128.6, 128.3, 128.0, 94.7, 94.2, 67.3, 67.0, 66.3, 65.7, 59.9, 59.0, 52.1, 51.8, 48.2, 27.4, 26.5, 24.4, 23.1; ESI-MS *m/z* 278 (M^++H, 100); HR-ESI-MS *m/z* 278.1407 (Calcd for $C_{15}H_{20}NO_4$: M^++H, 278.1392); *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.95; H, 7.09; N, 5.22. **2b**: $[\alpha]_D^{25}$ +46.2 (*c* = 1.00, $CHCl_3$); IR (neat) 2984, 1706, 1410, 1332, 1257, 1091 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.40-7.20 (5H, m), 5.20-5.05 (2H, m), 4.33 (0.4H, m), 4.23 (0.6H, m), 3.85 (1H, m), 3.76 (1H, m), 3.24 (0.4H, m), 3.15 (0.6H, m), 2.67 (1H, m), 2.60 (1H, m), 1.60-1.40 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.1, 152.1, 136.2, 136.0, 128.5, 128.1, 127.9, 94.5, 94.0, 67.4, 66.8, 63.1, 56.9, 56.2, 50.8, 44.0, 27.0, 26.2, 24.4, 23.0; ESI-MS *m/z* 278 (M^++H, 100); HR-ESI-MS *m/z* 278.1365 (Calcd for $C_{15}H_{20}NO_4$: M^++H, 278.1392); *Anal.* Calcd for $C_{15}H_{19}NO_4$: C, 64.97; H, 6.91; N, 5.05. Found: C, 65.03; H, 7.06; N, 4.98.

(*R*)-*tert*-Butyl 2,2-dimethyl-4-((*R*)-oxiran-2-yl)oxazolidine-3-carboxylate (2c). To a solution of carbamate **2a** (43.8 mg, 0.158 mmol) in MeOH (1.9 mL) were added Boc_2O (73.5 μL, 0.320 mmol) and 20% $Pd(OH)_2/C$ (21.9 mg). After stirring at room temperature for 12 h under H_2 atmosphere, the reaction mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane : AcOEt = 4 : 1) to give known carbamate **2c**[7] (3.0 mg, 7% yield) and recovered carbamate **2a** (20.0 mg, 46% recovered).

(*R*)-Benzyl 4-[(*S*)-1-(*tert*-butyldiphenylsilyloxy)-2-(methylamino)ethyl]-2,2-dimethyloxazolidine-3-carboxylate (3). A solution of epoxide **2a** (3.81 g, 13.7 mmol) in methylamine (41.9 mL, 411 mmol, 9.8 M in MeOH) was stirred at room temperature for 12 h. The reaction mixture was concentrated under reduced

pressure to give the crude aminoalcohol. The crude aminoalcohol was then used in the next reaction without purification.

To a solution of the above crude aminoalcohol in CH_2Cl_2 (6.85 mL) were added imidazole (4.66 g, 68.5 mmol) and TBDPSCl (17.9 mL, 68.5 mmol). After stirring at room temperature for 24 h, the reaction mixture was diluted with AcOEt and Et_2O, and then washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to give methylamine **3** (3.40 g, 45% yield, 2 steps) as a pale yellow oil. $[\alpha]_D^{23}$ +41.4 (*c* = 1.00, $CHCl_3$); IR (neat) 3339, 2933, 2875, 1703, 1406, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.75-7.6 (4H, m), 7.45-7.1 (11H, m), 5.12 (1.5H, m), 4.99 (0.5H, m), 4.25 (3H, m), 4.00 (1H, m), 2.57 (1H, m), 2.4-2.2 (4H, m), 1.7-1.4 (7H, m), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.8, 135.7, 134.5, 133.5, 129.6, 128.4, 128.1, 127.6, 94.8, 71.8, 71.6, 66.9, 64.0, 55.0, 35.9, 32.2, 27.1, 19.4; ESI-MS *m/z* 547 (M^++H, 100); HR-ESI-MS *m/z* 547.2996 (Calcd for $C_{32}H_{43}N_2O_4Si$: M^++H, 547.2992).

(*R*)-Benzyl 4-[(*S*)-1-(9*H*-fluoren-9-yl)-4,9,9-trimethyl-3-oxo-8,8-diphenyl-2,7-dioxa-4-aza-8-sila-decan-6-yl]-2,2-dimethyloxazolidine-3-carboxylate (4). To a solution of methylamine **3** (3.20 g, 5.86 mmol) in 1,4-dioxane (11.7 mL) were added 10% aqueous $NaHCO_3$ (11.7 mL) and FmocCl (1.82 g, 7.02 mmol). After stirring at room temperature for 30 min, the reaction mixture was diluted with AcOEt and Et_2O, and then washed with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 4 : 1) to give carbamate **4** (4.50 g, quantitative yield) as white crystals. mp 60-63 °C; $[\alpha]_D^{25}$ +8.94 (*c* = 1.00, $CHCl_3$); IR (KBr) 2933, 1701, 1405, 1092 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.8-7.2 (21H, m), 7.04 (2H, m), 5.2-4.6 (3H, m), 4.5-4.0 (5H, m), 4.0-3.3 (2H, m), 2.5-2.0 (2H, m), 1.8-1.2 (8H, m), 1.09 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.2, 152.9, 144.0, 143.8, 143.6, 141.3, 135.9, 129.8, 128.8, 128.5, 128.2, 128.0, 127.6, 124.9, 124.8, 119.9, 95.4, 67.8, 67.4, 67.1, 66.9, 63.2, 58.6, 50.8, 47.3, 32.9, 26.9, 25.6, 23.6, 19.1; ESI-MS *m/z* 769 (M^++H, 100), 547 (15); HR-ESI-MS *m/z* 769.3674 (Calcd for $C_{47}H_{53}N_2O_6Si$: M^++H, 769.3673); *Anal.* Calcd for $C_{47}H_{52}N_2O_6Si$: C, 73.41; H, 6.82; N, 3.64. Found: C, 73.19; H, 6.90; N, 3.64.

(9*H*-Fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)carbonyl)amino)-2-((*tert*-butyldiphenylsilyl)oxy)-4-hydroxybutyl)(methyl)carbamate (5). To a solution of acetonide **4** (1.99 g, 2.59 mmol) in MeCN (13.0 mL) was added $BiBr_3$ (117 mg, 0.26 mmol). After stirring at room temperature for 48 h, the reaction mixture was diluted with AcOEt and Et_2O, and then washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) to recover

acetonide **4** (603 mg, 30%) and to give alcohol **5** (1.17 g, 62% yield) as white crystals. mp 57-60 °C; $[\alpha]_D^{25}$ –7.21 (*c* = 1.00, $CHCl_3$); IR (KBr) 3443, 2931, 1700, 1455, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.8-7.1 (24H, m), 5.64 (0.75H, m), 5.41 (0.25H, m), 5.09 (2H, m), 4.57 (0.25H, m), 4.42 (0.25H, m), 4.32 (1.5H, m), 4.2-4.0 (3H, m), 3.98 (0.5H, m), 3.79 (0.5H, m), 3.62 (0.5H, m), 3.5-3.2 (1H, m), 2.92 (0.5H, m), 2.7-2.5 (1H, m), 2.40 (3H, m), 1.08 (9H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.0, 143.8, 141.2, 136.6, 136.6, 135.8, 135.8, 132.8, 132.1, 130.3, 130.2, 128.4, 128.0, 127.9, 127.8, 127.7, 127.5, 127.0, 125.0, 124.9, 119.9, 73.0, 67.6, 66.4, 61.6, 53.1, 50.8, 47.1, 33.8, 26.9, 19.3; ESI-MS *m/z* 729 (M^++H, 100), 507 (10); HR-ESI-MS *m/z* 729.3377 (Calcd for $C_{44}H_{49}N_2O_6Si$: M^++H, 729.3360); *Anal.* Calcd for $C_{44}H_{48}N_2O_6Si$: C, 72.40; H, 6.77; N, 3.96. Found: C, 72.50; H, 6.64; N, 3.84.

(9*H*-Fluoren-9-yl)methyl ((2*S*,3*R*)-3-(((benzyloxy)carbonyl)amino)-4-((*tert*-butyldimethylsilyl)oxy)-2-((*tert*-butyldiphenylsilyl)oxy)butyl)(methyl)carbamate (6). To a solution of aminoalcohol **5** (604 mg, 0.83 mmol) in DMF (1.66 mL) were added imidazole (170 mg, 2.49 mmol) and TBSCl (188 mg, 1.25 mmol). After stirring at room temperature for 10 min, the reaction mixture was diluted with Et_2O, and then washed with saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) to give TBS ether **6** (684 mg, 98% yield) as a colorless oil. $[\alpha]_D^{23}$ +2.02 (*c* = 0.89, $CHCl_3$); IR (neat) 3335, 2930, 1724, 1705, 1472, 1111 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.8-7.6 (6H, m), 7.55 (2H, d, *J* = 7.4 Hz), 7.5-7.25 (15H, m), 5.55 (0.5H, m), 5.2-5.0 (2.5H, m), 4.4-3.4 (8H, m), 2.82 (0.5H, m), 2.6-2.2 (3.5H, m), 1.09 (9H, s), 0.85 (9H, s), 0.02 (2H, s), 0.00 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.3, 143.9, 141.3, 135.9, 133.2, 129.9, 128.4, 127.7, 127.7, 127.6, 127.0, 125.0, 119.9, 69.1, 67.6, 66.3, 61.4, 55.6, 50.7, 47.2, 34.1, 26.9, 25.8, 19.3, 18.1, –5.5, –5.5; ESI-MS *m/z* 865 (M^++Na, 100), 843 (M^++H, 90), 621 (60); HR-ESI-MS *m/z* 843.4217 (Calcd for $C_{50}H_{63}N_2O_6Si_2$ M^++H, 843.4225).

(9*H*-Fluoren-9-yl)methyl (2*S*,3*R*)-3-amino-4-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyl-oxy)butyl(methyl)carbamate (7). To a solution of carbamate **6** (13.2 mg, 15.7 μmol) in AcOEt (1.57 mL) was added 10% Pd/C (13.2 mg). After stirring at room temperature for 5 h under H_2 atmosphere, the reaction mixture was filtered through a celite pad. The filtrate was concentrated under reduced pressure and the residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1) to give amine **7** (10.4 mg, 94% yield) as a pale yellow oil. $[\alpha]_D^{20}$ +6.47 (*c* = 0.90, $CHCl_3$); IR (neat) 3383, 2953, 2929, 2957, 1703, 1472, 1110 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.77 (2H, d, *J* = 7.6 Hz), 7.69 (4H, m), 7.56 (2H, m), 7.5-7.2 (10H, m), 4.35 (2H, m), 4.2-3.95 (2H, m), 3.7-3.2 (4H, m), 3.0-2.9 (1H, m), 2.64 (3H, s), 1.58 (2H, br s), 1.08 (9H, s), 0.9-0.8 (9H, m), 0.0- –0.1 (6H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 156.2, 144.0, 141.3, 135.9, 133.5, 129.8, 129.8, 127.7, 127.7, 127.6, 127.0, 125.0, 119.9, 72.7, 67.4, 64.6, 56.0, 50.7, 50.0,

47.3, 35.0, 29.7, 27.1, 25.9, 19.4, 18.1, –5.5; ESI-MS *m/z* 709 (M^++H, 100); HR-ESI-MS *m/z* 709.3824 (Calcd for $C_{42}H_{57}N_2O_4Si$: M^++H, 709.3857).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-((*E*)-3-Hydroxyprop-1-enyl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)-3-(4-methoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (9). To a cold (–78 °C) solution of α,β-unsaturated ester **8** (5.12 g, 14.5 mmol) in CH_2Cl_2 (145 mL) was added dropwise DIBAH (43.5 mL, 43.5 mmol, 1.0 M in toluene). After stirring at –78 °C for 5 min, Et_2O and Na_2SO_4•$10H_2O$ were added to the reaction mixture. The mixture was stirred at room temperature for 6 h and then filtered through a celite pad. The filtrate was concentrated under reduced pressure to give the crude aldehyde. The crude aldehyde was then used in the next reaction without purification.

To a cold (0 °C) solution of the above crude aldehyde in MeOH (19.3 mL) was added portionwise $NaBH_4$ (219 mg, 5.80 mmol). After stirring at room temperature for 6 h, saturated aqueous NH_4Cl was added to the reaction mixture. The mixture was diluted with $CHCl_3$, and then washed with H_2O and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude alcohol. The crude alcohol was then used in the next reaction without purification.

To a solution of the above crude alcohol in MeCN (30.4 mL) were added DBU (2.04 mL, 13.7 mmol) and MPMCl (1.48 mL, 10.9 mmol). The mixture was stirred at 60 °C for 3 h. The reaction mixture was cooled to room temperature, diluted with AcOEt and Et_2O, and then washed with 1M HCl, saturated aqueous $NaHCO_3$, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 4) to give MPM amide **9** (2.24 g, 36% yield, 3 steps) as pale yellow crystals. mp: 45-47 °C; $[\alpha]_D^{23}$ +52.9 (*c* = 1.00, $CHCl_3$); IR (KBr) 3446, 2990, 2932, 1712, 1668, 1513, 1455, 1386, 1249, 1087 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.7 Hz), 7.18 (1H, d, *J* = 8.0 Hz), 6.81 (2H, d, *J* = 8.7 Hz), 5.94 (1H, dt, *J* = 15.6, 4.6 Hz), 5.83 (1H, dd, *J* = 15.6, 7.5 Hz), 5.74 (1H, d, *J* = 8.0 Hz), 5.62 (1H, s), 5.01 (2H, s), 4.96 (1H, dd, *J* = 6.4, 1.5 Hz), 4.73 (1H, dd, *J* = 6.4, 4.3 Hz), 4.55 (1H, dd, *J* = 7.5, 4.3 Hz), 4.13 (2H, d, *J* = 4.2 Hz), 3.76 (3H, s), 1.91 (1H, br s), 1.56 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.5, 159.1, 150.5, 139.8, 134.1, 130.7, 128.7, 127.2, 114.4, 113.6, 102.0, 95.0, 87.9, 84.9, 84.2, 62.3, 55.2, 43.5, 27.1, 25.3; ESI-MS *m/z* 431 (M^++H, 100), 413 (20); HR-ESI-MS *m/z* 431.1801 (Calcd for $C_{22}H_{27}N_2O_7$: M^++H, 431.1818).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-((2*R*,3*S*)-3-(Hydroxymethyl)oxiran-2-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)-3-(4-methoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (10). To a cold (–20 °C) suspension of 4A molecular sieves (2.5 g) in CH_2Cl_2 (20 mL) were added L-(+)-DIPT (0.16 mL, 0.78 mmol) and Ti(O^iPr)$_4$ (0.15 mL, 0.52 mmol). After stirring at –20 °C for 10 min, TBHP (0.69 mL, 10.8 mmol, 15.6 M in CH_2Cl_2) was added to the mixture. After stirring for 30 min at the same temperature, a

solution of allylic alcohol **9** (2.24 g, 5.21 mmol) in CH_2Cl_2 (32.0 mL) was added to the mixture. The reaction temperature was slowly raised to room temperature. After stirring at the same temperature for 12 h, 30% NaOH solution in saturated aqueous NaCl was added to the reaction mixture. The mixture was diluted with Et_2O and stirred for 30 min. A mixture of $MgSO_4$ and celite (8 : 1) was then added. After stirring for 15 min, the mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 7) to give epoxyalcohol **10** (2.02 g, 87% yield) as white crystals. mp 52-55°C; $[\alpha]_D^{22}$ +5.95 (*c* = 1.04, $CHCl_3$); IR (KBr) 3458, 2989, 2937, 1711, 1669, 1514, 1456, 1388, 1249, 1081 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.42 (2H, d, *J* = 8.7 Hz), 7.24 (1H, d, *J* = 8.0 Hz), 6.82 (2H, d, *J* = 8.7 Hz), 5.78 (1H, d, *J* = 8.0 Hz), 5.73 (1H, d, *J* = 1.6 Hz), 5.03 (1H, d, *J* = 13.6 Hz), 4.99 (1H, d, *J* = 13.6 Hz), 4.91 (1H, dd, *J* = 6.6, 1.3 Hz), 4.77 (1H, m), 4.21 (1H, t, *J* = 4.0 Hz), 3.89 (1H, br d, *J* = 12.9 Hz), 3.78 (3H, s), 3.64 (1H, m), 3.35 (1H, m), 3.09 (1H, m), 1.90 (1H, br s), 1.54 (3H, s), 1.34 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.4, 159.1, 150.6, 139.4, 130.7, 128.7, 114.5, 113.7, 102.3, 94.7, 86.7, 84.8, 79.9, 60.7, 56.6, 55.2, 53.9, 43.5, 27.0, 25.2; ESI-MS *m/z* 447 (M^++H, 100); HR-ESI-MS *m/z* 447.1799 (Calcd for $C_{22}H_{27}N_2O_8$: M^++H, 447.1767).

(9*H*-Fluoren-9-yl)methyl (2*S*,3*R*)-4-(*tert*-butyldimethylsilyloxy)-2-(*tert*-butyldiphenylsilyloxy)-3-((2*R*,3*S*)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(3-(4-methoxybenzyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)oxirane-2-carboxamido)butyl(methyl)carbamate (11).

To a cold (0 °C) solution of alcohol **10** (241 mg, 0.540 mmol) in acetone (1.2 mL) were added 5% aqueous $NaHCO_3$ (1.5 mL), KBr (6.43 mg, 54.0 μmol), TEMPO (8.44 mg, 54.0 μmol), and NaClO (2.08 mL, 1.62 mmol, 0.78 M in H_2O). After stirring at room temperature for 2 h, the reaction mixture was diluted with Et_2O and AcOEt, and then washed with saturated aqueous NaH_2PO_4, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the crude carboxylic acid. The crude carboxylic acid was then used in the next reaction without purification.

To a solution of the above crude carboxylic acid and amine **7** (255 mg, 0.54 mmol) in THF (0.72 mL) were added EDC (104 mg, 0.54 mmol) and HOBt (73.0 mg, 0.54 mmol). After stirring at room temperature for 12 h, the reaction mixture was diluted with Et_2O and AcOEt, and then washed with saturated aqueous $NaHCO_3$, saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1) to give epoxyamide **11** (314 mg, 75% yield) as a colorless oil. $[\alpha]_D^{22}$ +20.2 (*c* = 0.97, $CHCl_3$); IR (neat) 2953, 2930, 1698, 1671, 1455, 1249, 1105 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.8-7.6 (6H, m), 7.52 (2H, d, *J* = 7.4 Hz), 7.5-7.2 (13H, m), 6.82 (2H, d, *J* = 8.6 Hz), 5.80 (1H, br s), 5.74 (1H, d, *J* = 8.0 Hz), 5.08 (1H, d, *J* = 13.6 Hz), 4.96 (1H, d, *J* = 13.6 Hz), 4.79 (1H, m), 4.65 (1H, m), 4.4-4.1 (6H, m), 3.76 (3H, s), 3.75-3.6 (3H, m), 3.4-3.2 (3H, m), 2.85-2.5 (1H, m), 2.46 (3H, s),

1.55 (3H, s), 1.33 (3H, s), 1.08 (9H, s), 0.83 (9H, s), 0.00 (3H, s), –0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.6, 162.3, 159.1, 156.6, 150.6, 143.9, 141.2, 138.5, 136.0, 135.9, 133.4, 132.9, 130.8, 130.0, 129.9, 128.8, 127.8, 127.7, 127.6, 127.0, 127.0, 124.9, 119.9, 114.9, 113.7, 102.5, 93.7, 93.7, 85.4, 84.8, 79.2, 68.8, 67.7, 60.8, 57.0, 55.2, 53.3, 53.3, 50.7, 47.1, 43.6, 34.1, 29.7, 27.1, 26.9, 25.8, 25.3, 19.3, 18.0, –5.5, –5.6; ESI-MS *m/z* 1151 (M^++H, 100), 929 (90); HR-ESI-MS *m/z* 1151.5270 (Calcd for $C_{64}H_{79}N_4O_{12}Si_2$: M^++H, 1151.5233); *Anal.* Calcd for $C_{64}H_{78}N_4O_{12}Si_2$: C, 66.76; H, 6.83; N, 4.87. Found: C, 66.62; H, 6.99; N, 4.90.

(2*R*,3*S*)-*N*-((5*S*,6*R*)-2,2,9,9,10,10-Hexamethyl-5-((methylamino)methyl)-3,3-diphenyl-4,8-dioxa-3,9-disilaundecan-6-yl)-3-((3a*R*,4*R*,6*R*,6a*R*)-6-(3-(4-methoxybenzyl)-2,4-dioxo-3,4-dihydropyrimidin-1(2*H*)-yl)-2,2-dimethyltetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl)oxirane-2-carboxamide (12). To a solution of epoxyamide **11** (220 mg, 0.191 mmol) in CH_2Cl_2 (0.95 mL) was added Et_3N (0.95 mL). After stirring at room temperature for 4 days, the reaction mixture was diluted with Et_2O and AcOEt, and then washed with saturated aqueous NH_4Cl, H_2O, and saturated aqueous NaCl. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (AcOEt) to give amine **12** (156 mg, 90% yield) as a pale yellow oil. $[\alpha]_D^{22}$ +8.00 (*c* = 0.93, $CHCl_3$); IR (neat) 3329, 2954, 2929, 2856, 1713, 1671, 1514, 1105 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (1H, d, *J* = 7.7 Hz), 7.65 (4H, m), 7.5-7.3 (9H, m), 7.22 (1H, d, *J* = 8.0 Hz), 6.82 (2H, d, *J* = 8.7 Hz), 5.81 (1H, d, *J* = 1.8 Hz), 5.77 (1H, d, *J* = 8.0 Hz), 5.09 (1H, d, *J* = 13.6 Hz), 4.97 (1H, d, *J* = 13.6 Hz), 4.86 (1H, d, *J* = 6.5 Hz), 4.72 (1H, m), 4.27 (1H, m), 4.16 (1H, m), 4.08 (1H, m), 3.77 (3H, s), 3.64 (1H, dd, *J* = 10.2, 4.6 Hz), 3.40 (2H, m), 3.33 (1H, m), 2.64 (2H, d, *J* = 3.2 Hz), 2.24 (3H, s), 1.56 (3H, s), 1.35 (3H, s), 1.06 (9H, s), 0.77 (9H, s), –0.07 (3H, s), –0.07 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 162.3, 159.1, 150.7, 138.7, 135.8, 135.6, 133.9, 133.1, 130.8, 129.9, 129.8, 128.7, 127.7, 127.7, 114.8, 113.7, 102.5, 94.0, 85.6, 84.8, 79.3, 69.8, 61.9, 57.0, 55.4, 55.2, 53.4, 53.3, 43.6, 36.5, 27.1, 27.0, 25.7, 25.3, 19.3, 18.0, –5.5, –5.8; ESI-MS *m/z* 929 (M^++H, 100), 457 (35); HR-ESI-MS m/z 929.4568 (Calcd for $C_{49}H_{69}N_4O_{10}Si_2$: M^++H, 929.4552).

1-((3a*R*,4*R*,6*R*,6a*R*)-6-((*R*)-((2*S*,5*R*,6*S*)-5-((*tert*-Butyldimethylsilyloxy)methyl)-6-(*tert*-butyldiphenylsilyloxy)-1-methyl-3-oxo-1,4-diazepan-2-yl)(hydroxy)methyl)-2,2-dimethyltetrahydrofuro[3,4-*d*]-[1,3]dioxol-4-yl)-3-(4-methoxybenzyl)pyrimidine-2,4(1*H*,3*H*)-dione (13). A solution of epoxyamine **12** (6.4 mg, 6.89 μmol) in THF (6.9 mL) was refluxed for 3 days. After cooling to room temperature, the mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1) to give diazepanone **13** (4.2 mg, 66% yield) as a colorless oil. $[\alpha]_D^{22}$ –17.0 (*c* = 0.77, $CHCl_3$); IR (neat) 2953, 2931, 2857, 1707, 1668, 1456, 1249, 1101 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.8-7.65 (5H, m), 7.5-7.3 (9H, m), 6.81 (2H, d, *J* = 8.6 Hz), 6.04 (1H, d, *J* = 2.5 Hz),

5.73 (1H, d, *J* = 8.1 Hz), 5.10 (1H, d, *J* = 13.6 Hz), 4.98 (1H, d, *J* = 13.6 Hz), 4.93 (1H, m), 4.68 (1H, m), 4.65 (1H, m), 4.32 (1H, br s), 4.07 (1H, m), 3.94 (1H, m), 3.76 (3H, s), 3.74 (1H, m), 3.64 (2H, m), 3.39 (1H, m), 2.9-2.8 (2H, m), 2.25 (3H, s), 1.61 (3H, s), 1.39 (3H, s), 1.05 (9H, s), 0.88 (9H, s), 0.05 (3H, s), 0.03 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.6, 162.7, 159.0, 151.0, 138.4, 135.9, 135.7, 133.5, 132.4, 130.8, 130.3, 130.0, 129.1, 128.0, 127.8, 113.9, 113.6, 101.7, 92.0, 86.4, 85.6, 78.9, 73.0, 68.1, 66.0, 63.2, 58.3, 55.3, 55.2, 43.5, 35.0, 27.4, 26.8, 25.9, 25.6, 19.5, 18.3, –5.2, –5.5; ESI-MS *m/z* 929 (M^++H, 100), 457 (70); HR-ESI-MS *m/z* 929.4512 (Calcd for $C_{49}H_{69}N_4O_{10}Si_2$: M^++H, 929.4552).

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