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A Simple Method for Deprotection of the *N*- and *O*-Carbobenzoxy Groups and *N*-Methylation of the Desosamine Sugar Moiety of Ketolides

Application to the Synthesis of Ketolide Analogues with Various 9-Iminoether Moieties and Their Antibacterial Activities

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Abstract A simple synthetic method for deprotection of the *N*- and *O*-carbobenzoxy groups (Cbz) of the desosamine sugar moiety of ketolides is reported. This deprotection method is applicable to the synthesis of a variety of ketolide analogues with various 9-iminoether moieties in good to moderate yield. Among the ketolide derivatives prepared by this method, compound **7g** with a quinoline-6-yl moiety showed potent activity against erythromycin-resistant pathogens as well as *Haemophilus influenzae*.

Keywords ketolide, antibacterial activity, carbobenzoxy, deprotection, Lewis acid

Introduction

For macrolide analogue synthesis, carbobenzoxy (Cbz) groups are usually used to protect the desosamine sugar moiety accompanied with *N*-demethylation and their deprotection is usually accomplished by catalytic hydrogenation [1～3]. However, it is difficult to use hydrogenation with Pd/C for compounds having substituents with poisonous activity against Pd/C, such as thiophene or quinoline, or for compounds with alkene or alkyne, which are susceptible to hydrogenation. A Lewis acid, such as TMS-I (iodotrimethylsilane), can also be used for deprotection of the Cbz group [4～8], but using TMS-I for the deprotection of ketolide analogues often leads to a low yield of the deprotected products. We report a simple method for deprotection of the *N*- and *O*-Cbz groups and its application to the synthesis of ketolide analogues.

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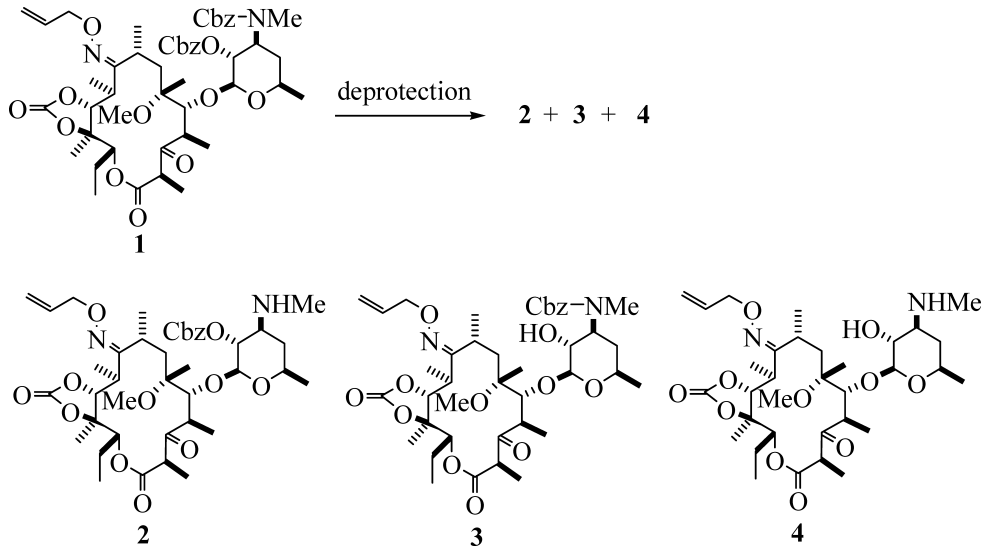
Synthesis

Scheme 1 shows the deprotection scheme of Cbz-protected ketolide **1** [3] giving the desired deprotected product **4** along with the half-deprotected intermediates **2** and **3**. The results of deprotection with various reagents and conditions are summarized in Table 1. Deprotected product **4** was obtained in 26% yield using 2 eq of TMS-I along with intermediate **2** (48%) (run 1). With 10 eq of TMS-I, the desired product **4** was obtained in 47% yield as a sole product (run 2). These results suggest that the *N*-Cbz group is readily deprotected with TMS-I and requires a few equivalents (more than 2 eq) of TMS-I for deprotection of the *O*-Cbz group. If $AlCl_3$/anisole is used, only the *O*-deprotected intermediate **3** is obtained in a good yield (run 3), suggesting that $AlCl_3$ is a suitable reagent for deprotection of the *O*-Cbz group. These results led us to combine the two reagents, TMS-I and $AlCl_3$ (run 4). Treatment of **1** with TMS-I (4 eq) at room temperature followed by $AlCl_3$/anisole (4 eq) at 0°C gave the desired deprotected product **4** in almost quantitative yield. The reaction became complicated if $AlCl_3$/anisole was used prior to TMS-I, presumably due to the excess TMS-I would cause decomposition of the compound **3** or **4**.

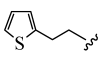
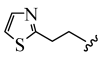
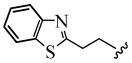
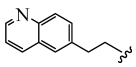
Table 1 Reaction conditions and yields of compounds **2**, **3** and **4**

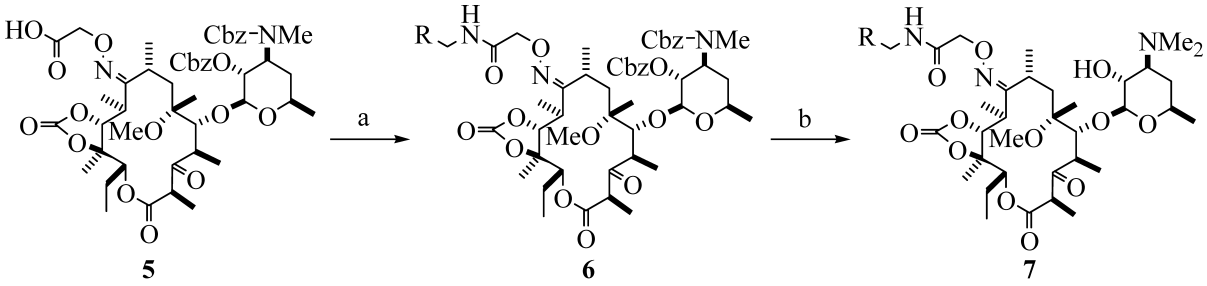
Run	Reagent	Molar equiv	Solvent	Temp (°C)	Time (h)	Yield (%)		
						2	**3**	**4**
1	TMSI	2	CH_2Cl_2	r.t.	20	48	0	26
2	TMSI	10	CH_2Cl_2	r.t.	3	0	0	47
3	$AlCl_3$/anisole	4	CH_2Cl_2	0	0.8	0	93	0
4	TMSI, $AlCl_3$/anisole	4, 4	CH_2Cl_2	0	1.3, 0.5	0	0	99



Scheme 1

Table 2 Yields of **7** from **6** by the deprotection method with TMSI/$AlCl_3$, anisole and subsequent *N*-methylation

Product	**7a**	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**
R							
Yield (%)	65	64	62	83	74	84	68

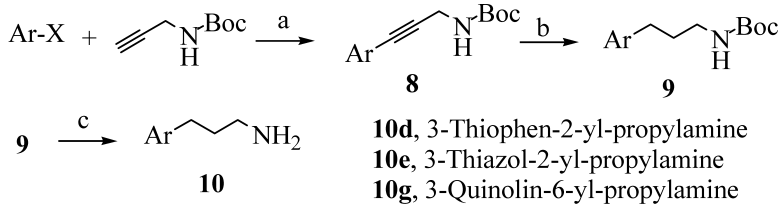


Reagents and conditions : (a) $(ClCO)_2$, cat. DMF, RCH_2NH_2 (b) (1)TMSI, $AlCl_3$/anisole (2) HCOOH, HCHO aq

Scheme 2

Table 3 *In vitro* antibacterial activities of compounds **7a**~**7g**

Strain	MIC [μg/ml]							
	7a	**7b**	**7c**	**7d**	**7e**	**7f**	**7g**	Telithromycin
Staphylococcus aureus Smith	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Sta. aureus SR17347 (EM-R)	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.39
Streptococcus pneumoniae Type I	0.025	0.025	0.025	0.05	0.025	0.0125	0.0125	0.0125
Str. pneumoniae SR16651 (EM-R)	50	50	25	25	>100	0.78	0.05	0.2
Haemophilus influenzae SR88562	12.5	6.25	6.25	6.25	3.13	3.13	1.56	1.56



Reagents and conditions: (a) NEt_3, CuI, cat. $Cl_2Pd(PPh_3)_2$; (b) H_2, 5%Pd/C; (c) CF_3CO_2H

Scheme 3

The above-mentioned deprotection method is effective for preparing a variety of ketolides by combination with a subsequent *N*-methylation procedure (Scheme 2). As shown in Table 2, ketolides with alkene, alkyne or heteroaromatics can be prepared in moderate yield from **6**, which is readily accessible by amidation from the key intermediate **5** [9]. The key intermediate **5** is also readily accessible by oxidation of C-9 allyl iminoether group from compound **1** [3].

3-Aryl-propylamines used for the synthesis of **6** were prepared as shown in Scheme 3. Other amines not listed in Scheme 3 were commercially purchased or prepared by a known method.

Results and Discussion

All the ketolides prepared were evaluated *in vitro* by the standard agar dilution method with various strains. Table 3 shows the antibacterial activities of the ketolides prepared along with telithromycin [10] as a reference compound against erythromycin (EM)-susceptible and -resistant *Staphylococcus aureus* and *Streptococcus pneumoniae* including one strain of *Haemophilus influenzae*. *Sta. aureus* SR17347 is an inducibly MLS_B resistant strain bearing an *erm*C gene, and *Str. pneumoniae* is also an inducibly MLS_B resistant strain bearing an *erm*B gene. All ketolides in Table 3 showed potent antibacterial activities against both EM-susceptible and -resistant *S. aureus* and EM-susceptible *Str. pneumoniae*. As for the analogues **7a**, **7b** and **7c** bearing the phenyl group, all of them lost their activity against EM-resistant *Str. pneumoniae* compared to the analogue with phenylpropylamide group (its activity not listed in Table 3). Although compound **7d** and **7e** bearing a five-membered heteroaromatic group were also almost inactive against EM-resistant *Str. pneumoniae*, compounds bearing 9~10-membered fused bicyclic heteroaromatics showed potent antibacterial activity. Among the analogues prepared, compound **7g** with a quinoline-6-yl moiety was found to have the most potent activity against EM-resistant *Str. pneumoniae* as well as *H. influenzae*.

The deprotection and subsequent *N*-methylation method described herein enabled us to prepare a variety of ketolide analogues and should also contribute to the synthesis of novel ketolide derivatives.

Experimental

Infrared (IR) spectra were taken on a JASCO FT/IR-700 spectrometer. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75 MHz) spectra were recorded on a Varian Gemini-300. Chemical shifts are reported in ppm using tetramethylsilane (TMS) as an internal standard. HR-MS (FAB)/MS (FAB) were

recorded on a JEOL LMS-SX/SX 102A. Analytical thin layer chromatography (TLC) was carried out on Merck precoated TLC plates silica gel 60 F_{254} and visualized with UV light or 10% H_2SO_4 containing 5% ammonium molybdate and 0.2% ceric sulfate. Flush chromatography was performed with Merck silica gel 60 (230～400 mesh).

Measurement of *in Vitro* Antibacterial Activity

MICs were determined by a serial two-fold dilution method in Sensivity Disk Agar-N (Nissui Pharmaceutical, Tokyo, Japan). The overnight cultures of antibacterial strains in Mueller Hinton broth (Becton Dickinson) were diluted to about 10^6 CFU/ml. Bacterial suspensions of 1 μl were spotted onto agar plates containing various concentrations of an antibiotic and incubated for 20 hours at 37°C before the MICs were scored.

Preparation of 4 from 1

Compound **1** [3] (277 mg, 0.3 mmol) was dissolved with CH_2Cl_2 (3 ml) and TMS-I (160 μl, 1.2 mmol) was added to the solution at room temperature under N_2 atmosphere. After being stirred for 80 minutes at room temperature, the reaction mixture was cooled to 0°C. To this was added $AlCl_3$ (160 mg, 1.2 mmol) and anisole (3 ml) dissolved in CH_2Cl_2 (3 ml) with stirring for 30 minutes at 0°C. The reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted twice with $CHCl_3$ - MeOH (10 : 1) and the combined organic layer was washed with diluted aqueous $Na_2S_2O_3$ and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant residue was purified by column chromatography on silicagel to give 196 mg of compound **4** as a colorless foam (99%).

MS (FAB): 655^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{33}H_{55}N_2O_{11}$ 655.3806 found 655.3797; IR ($CHCl_3$) 3691, 3604, 3363, 1797, 1752, 1456, 1382; ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (3H, t, J=7.5 Hz), 1.01 (3H, d, J=7.0 Hz), 1.20 (3H, d, J=7.6 Hz), 1.24 (3H, d, J=7.0 Hz), 1.29 (3H, d, J=6.1 Hz), 1.30 (1H, m), 1.36 (3H, s), 1.37 (3H, d, J=6.7 Hz), 1.56 (3H, s), 1.57 (1H, m), 1.60 (1H, m), 1.64 (1H, m), 1.92 (1H, m), 2.10 (1H, m), 2.52 (1H, q, J=7.0 Hz), 2.67 (3H, s), 2.68 (3H, s), 3.04 (1H, m), 3.05 (1H, m), 3.60 (1H, m), 3.60 (1H, m), 3.80 (1H, d, J=6.6 Hz), 4.19 (1H, d, J=7.6 Hz), 4.33 (1H, d, J=7.3 Hz), 4.53 (2H, m), 4.59 (1H, dd, J=10.1 and 7.3 Hz), 4.79 (1H, s), 5.05 (1H, dd, J=10.2 and 2.8 Hz), 5.16 (1H, m), 5.27 (1H, m), 6.00 (1H, m); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.41, 13.25, 14.52, 15.46, 15.58, 18.84, 19.64, 20.71, 22.46, 26.06, 31.20, 33.14, 34.42, 36.13, 47.23, 49.60, 51.09, 60.55, 68.40, 71.43, 74.58, 76.47, 78.11, 78.73, 82.80, 84.51, 102.09, 116.96, 134.28, 154.16, 163.69, 168.69, 203.80.

Preparation of Compound 7a

1. Amidation

To a solution of **5** (300 mg, 0.318 mmol) in toluene (6 ml) was added DMF (2 μl, 0.03 mmol) and oxalyl chloride (35 μl, 0.38 mmol) at room temperature, and the reaction mixture was stirred for 30 minutes at room temperature. To this solution, 3-phenylpropargylamine (83 mg, 0.64 mmol) in THF (3 ml) was added, and the reaction mixture was stirred another 30 minutes. The reaction mixture was quenched with saturated aqueous NH_4Cl and extracted with AcOEt (20 ml). The aqueous layer was extracted with AcOEt (20 ml) and the combined organic layer was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silicagel (*n*-hexane/AcOEt=4/1～2/1) to give 297 mg of compound **6a** bearing an *N*-phenypropropargylacetamide group as a colorless foam (89%).

MS (FAB): 1076^+ ($M+Na^+$). HR-MS (FAB): calcd for $C_{57}H_{71}N_3O_{16}Na$ 1076.4732 found 1076.4723; IR (KBr): 3440, 3063, 3032, 2974, 2938, 2880, 1811, 1752, 1701, 1521, 1490, 1455, 1407, 1382, 1330, 1287, 1253, 1167, 1113, 1068, 1003 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 2.70 (3H, s), 2.80 and 2.84 (3H, two s); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.1, 12.9, 13.8, 15.2, 15.3, 18.7, 19.7, 20.5, 22.2, 26.2, 28.9, 29.5, 33.2, 35.6, 36.1, 37.5, 46.7, 46.8, 49.6, 50.8, 54.7, 67.0, 67.1, 68.6, 69.2, 69.4, 72.6, 74.5, 75.9, 76.0, 78.0, 82.1, 82.8, 84.3, 84.4, 100.3, 122.4, 127.3, 127.4, 127.6, 127.7, 127.9, 128.0, 128.1, 128.2, 131.6, 135.1, 135.3, 136.3, 153.5, 154.1, 154.2, 155.7, 156.1, 167.2, 168.6, 169.6, 203.3, 203.6.

2. Deprotection and *N*-methylation

This colorless foam **6a** (197 mg, 0.187 mmol) bearing an *N*-phenypropropargylacetamide was dissolved with CH_2Cl_2 (3 ml), and TMS-I (106 μl, 0.75 mmol) was added to the solution at room temperature under N_2 atmosphere. After being stirred for 1 hour at room temperature, the reaction mixture was cooled to 0°C. To this was added $AlCl_3$ (99 mg, 0.75 mmol) and anisole (1 ml) dissolved in CH_2Cl_2 (1 ml) with stirring for 30 minutes at 0°C. The reaction mixture was diluted with H_2O (0.3 ml) and *n*-hexane (8 ml) at 0°C, and the precipitate was collected, washed three times with *n*-hexane and dissolved with MeOH - $CHCl_3$ (1 ml - 5 ml). This solution was poured into saturated aqueous $NaHCO_3$ and extracted twice with $CHCl_3$ - MeOH (10 : 1), and the combined organic layer was washed with diluted aqueous $Na_2S_2O_3$, brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The resultant residue was dissolved with MeOH (3 ml), then 98%-HCO_2H (15 μl) and 35% aqueous HCHO (94 μl) were added with stirring at 75°C for 2 hours. After cooling to room temperature, the

reaction mixture was poured into saturated aqueous $NaHCO_3$ and extracted with AcOEt (20 ml×2). The combined extract was washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silicagel ($CHCl_3$/MeOH=80/1～20/1) to give 100 mg of compound **7a** as a colorless foam (65%).

MS (FAB): 800^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{42}H_{62}N_3O_{12}$ 800.4334 found 800.4336; IR (KBr): 3442, 2974, 2938, 2879, 2839, 2785, 1811, 1752, 1716, 1683, 1599, 1522, 1490, 1456, 1381, 1361, 1324, 1304, 1282, 1257, 1233, 1167, 1141, 1109, 1078, 1047, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.82 (3H, t, *J*=7.5 Hz), 1.02 (3H, d, *J*=6.9 Hz), 1.22 (3H, d, *J*=6.0 Hz), 1.26 (3H, d, *J*=6.9 Hz), 1.28 (3H, d, *J*=6.6 Hz), 1.35 (3H, d, *J*=6.6 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.20～1.94 (6H, m), 2.27 (6H, s), 2.47 (1H, m), 2.67 (1H, q, *J*=7.2 Hz), 2.74 (3H, s), 3.03 (1H, quintet, *J*=7.5 Hz), 3.18 (1H, dd, *J*=7.8 and 10.2 Hz), 3.50～3.75 (3H, m), 3.83 (1H, q, *J*=6.9 Hz), 4.21 (1H, d, *J*=7.8 Hz), 4.30 (1H, d, *J*=7.2 Hz), 4.31 (2H, dd, *J*=6.0 and 9.0 Hz), 4.52 (2H, s), 4.86 (1H, s), 4.98 (1H, dd, *J*=3.0 and 10.2 Hz), 7.06 (1H, br t, *J*=5.4 Hz), 7.24～7.32 (3H, m), 7.38～7.46 (2H, m); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.1, 12.9, 14.3, 15.3, 15.4, 18.8, 19.8, 21.1, 22.2, 26.4, 28.2, 29.5, 33.3, 38.0, 40.2, 47.5, 49.8, 51.0, 65.8, 69.4, 70.2, 72.8, 76.0, 78.3, 78.5, 82.3, 83.0, 84.5, 103.7, 122.7, 128.1, 128.2, 131.8, 153.8, 167.8, 169.0, 170.0, 204.0.

Preparation of Compounds 7b, 7c, 7d, 7e, 7f, and 7g

Compound **7b**, **7c**, **7d**, **7e**, **7f** and **7g** were prepared by the same procedure described for the synthesis of **7a** with cinnamylamine, (*Z*)-3-phenyl-allyamine [11], **10d**, **10e**, 3-benzothiazol-2-yl-propylamine [12] and **10g**, respectively.

Compound **7b**

MS (FAB): 802 ($M+H^+$). HR-MS (FAB): calcd for $C_{42}H_{64}N_3O_{12}$ 802.4490 found 802.4489; IR (KBr): 3436, 2974, 2938, 2879, 2785, 1811, 1752, 1717, 1677, 1525, 1495, 1455, 1380, 1362, 1324, 1304, 1283, 1257, 1233, 1167, 1141, 1109, 1078, 1047, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.75 (3H, t, *J*=7.2 Hz), 0.99 (3H, d, *J*=7.2 Hz), 1.23 (3H, d, *J*=6.0 Hz), 1.24 (3H, d, *J*=6.9 Hz), 1.27 (3H, d, *J*=7.5 Hz), 1.35 (3H, d, *J*=6.6 Hz), 1.38 (3H, s), 1.52 (3H, s), 1.20～1.80 (5H, m), 2.27 (6H, s), 2.47 (1H, m), 2.54 (1H, q, *J*=7.2 Hz), 2.70 (3H, s), 3.00 (1H, quintet, *J*=7.5 Hz), 3.18 (1H, dd, *J*=7.5 and 10.2 Hz), 3.48～3.73 (4H, m), 3.80 (1H, q, *J*=6.6 Hz), 3.92 (1H, m), 4.13 (1H, m), 4.21 (1H, d, *J*=7.8 Hz), 4.30 (1H, d, *J*=7.2 Hz), 4.50 and 4.52 (2H, ABq, *J*=15.3 Hz), 4.79 (1H, s), 4.84 (1H, dd, *J*=3.0 and 10.5 Hz), 6.26 (1H, dt, *J*=6.6 and 15.9 Hz), 6.56 (1H, *J*=15.9 Hz), 7.05 (1H, br t, *J*=5.4 Hz), 7.15～7.42 (5H, m); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.0, 12.9, 14.3, 15.3, 15.5, 18.8, 19.9, 21.1, 22.1, 26.3, 28.2, 33.2, 38.0, 40.2, 41.4, 47.5, 49.8, 51.0, 65.9, 69.5, 70.2, 73.0, 75.9, 78.4, 78.5, 82.4, 84.5, 103.7, 125.0, 126.5, 127.4, 128.4, 132.6, 136.6, 153.7, 167.6, 169.0, 170.2, 204.0.

Compound **7c**

MS (FAB): 802^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{42}H_{64}N_3O_{12}$ 802.4490 found 802.4493; IR (KBr): 3436, 3055, 2973, 2938, 2879, 2785, 1811, 1751, 1717, 1676, 1527, 1494, 1456, 1381, 1363, 1325, 1304, 1283, 1257, 1233, 1166, 1141, 1109, 1078, 1047, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, *J*=7.5 Hz), 0.99 (3H, d, *J*=6.9 Hz), 1.24 (6H, d, *J*=6.6 Hz), 1.28 (3H, d, *J*=7.5 Hz), 1.37 (3H, s), 1.38 (3H, d, *J*=6.9 Hz), 1.55 (3H, s), 1.20～1.97 (5H, m), 2.28 (6H, s), 2.48 (1H, m), 2.55 (1H, q, *J*=6.9 Hz), 2.67 (3H, s), 3.02 (1H, quintet, *J*=7.8 Hz), 3.07 (1H, br s), 3.18 (1H, dd, *J*=7.8 and 10.2 Hz), 3.50～3.73 (2H, m), 3.83 (1H, q, *J*=7.2 Hz), 4.16～4.25 (2H, m), 4.21 (1H, d, *J*=7.8 Hz), 4.30 (1H, d, *J*=7.2 Hz), 4.48 (2H, s), 4.81 (1H, s), 4.99 (1H, dd, *J*=2.7 and 10.2 Hz), 5.69 (1H, dt, *J*=6.9 and 11.7 Hz), 6.58 (1H, *J*=11.7 Hz), 6.91 (1H, br t, *J*=5.4 Hz), 7.19～7.38 (5H, m); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.3, 13.0, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.3, 26.3, 28.2, 33.2, 37.4, 38.0, 40.2, 47.6, 49.8, 51.1, 65.9, 69.5, 70.2, 72.9, 76.1, 78.3, 78.6, 82.3, 84.5, 103.7, 127.0, 127.8, 128.2, 128.7, 131.5, 136.3, 153.7, 167.5, 169.0, 170.1, 204.0.

Compound **7d**

MS (FAB): 810^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{40}H_{64}N_3O_{12}S_1$ 810.4211 found 810.4219; IR ($CHCl_3$): 3424, 3350, 3016, 2970, 2934, 2870, 1805, 1751, 1714, 1663, 1537, 1454, 1381, 1361, 1345, 1321, 1305, 1282, 1255, 1232, 1220, 1165, 1139, 1107, 1075, 1046, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, *J*=7.5 Hz), 1.02 (3H, d, *J*=6.6 Hz), 1.25 (3H, d, *J*=6.9 Hz), 1.26 (3H, d, *J*=7.5 Hz), 1.28 (3H, d, *J*=8.1 Hz), 1.37 (3H, d, *J*=6.6 Hz), 1.38 (3H, s), 1.56 (3H, s), 1.20～2.00 (8H, m), 2.33 (6H, s), 2.56 (2H, m), 2.69 (3H, s), 2.88 (2H, t, *J*=7.8 Hz), 3.03 (1H, quintet, *J*=7.8 Hz), 3.19～3.30 (2H, m), 3.36～3.47 (1H, m), 3.51～3.74 (3H, m), 3.84 (1H, q, *J*=6.9 Hz), 4.22 (1H, d, *J*=7.8 Hz), 4.31 (1H, d, *J*=6.9 Hz), 4.46 (2H, s), 4.84 (1H, s), 5.03 (1H, dd, *J*=2.4 and 10.2 Hz), 6.82 (1H, d, *J*=3.1 Hz), 6.89 (1H, dd, *J*=3.1 and 5.1 Hz), 6.94 (1H, br t, *J*=5.7 Hz), 7.09 (1H, dd, *J*=1.2 and 5.1 Hz); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 14.3, 15.3, 15.5, 18.8, 19.9, 21.1, 22.3, 26.3, 27.2, 28.6, 31.2, 33.2, 38.0, 38.5, 40.2, 47.5, 49.7, 51.0, 65.8, 69.3, 70.2, 72.9, 76.1, 78.4, 78.5, 82.3, 84.6, 103.5, 122.9, 124.3, 126.7, 144.2, 153.8, 167.6, 169.2, 170.4, 203.9.

Compound **7e**

MS (FAB): 811^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{39}H_{63}N_4O_{12}S_1$ 811.4163 found 811.4166; IR (KBr): 3433, 3080, 2973, 2938, 2878, 2784, 1809, 1751, 1716, 1673, 1533, 1504, 1455, 1380, 1363, 1323, 1305, 1284, 1257, 1233, 1168, 1141, 1109, 1078, 1047, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.90 (3H, t, J=7.5 Hz), 1.02 (3H, d, J=6.9 Hz), 1.24 (3H, d, J=6.3 Hz), 1.26 (3H, d, J=5.4 Hz), 1.28 (3H, d, J=6.9 Hz), 1.34 (3H, d, J=6.9 Hz), 1.36 (3H, s), 1.56 (3H, s), 1.20～2.00 (6H, m), 2.07 (2H, quintet, J=7.5 Hz), 2.27 (6H, s), 2.46 (1H, m), 2.57 (1H, q, J=6.6 Hz), 2.69 (3H, s), 3.09 (2H, t, J=7.8 Hz), 3.18 (1H, dd, J=7.5 and 10.2 Hz), 2.95～3.75 (5H, m), 3.84 (1H, q, J=7.2 Hz), 4.22 (1H, d, J=7.8 Hz), 4.30 (1H, d, J=7.2 Hz), 4.46 (2H, s), 4.84 (1H, s), 5.06 (1H, dd, J=2.4 and 10.2 Hz), 7.03 (1H, br t, J=5.4 Hz), 7.17 (1H, d, J=3.6 Hz), 7.65 (1H, d, J=3.6 Hz); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.3, 12.9, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.3, 26.4, 28.2, 29.5, 30.4, 33.2, 38.0, 38.2, 40.2, 47.6, 49.7, 51.0, 65.8, 69.5, 70.3, 72.9, 76.1, 78.4, 78.6, 82.4, 84.6, 103.7, 118.1, 142.2, 153.8, 167.6, 169.2, 170.1, 170.4, 203.9.

Compound **7f**

MS (FAB): 861^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{43}H_{65}N_4O_{12}S_1$ 861.4320 found 861.4329; IR ($CHCl_3$): 3424, 3348, 2970, 2934, 2870, 2830, 1805, 1751, 1714, 1665, 1536, 1454, 1381, 1361, 1345, 1306, 1282, 1232, 1220, 1165, 1139, 1107, 1075, 1046, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.87 (3H, t, J=7.5 Hz), 1.02 (3H, d, J=6.6 Hz), 1.23 (3H, d, J=6.0 Hz), 1.27 (3H, d, J=6.6 Hz), 1.28 (3H, d, J=7.2 Hz), 1.36 (3H, d, J=6.6 Hz), 1.39 (3H, s), 1.56 (3H, s), 1.20～1.98 (6H, m), 2.16 (2H, quintet, J=7.2 Hz), 2.27 (6H, s), 2.45 (1H, m), 2.57 (1H, q, J=6.9 Hz), 2.71 (3H, s), 2.95～3.75 (6H, m), 3.18 (2H, t, J=7.5 Hz), 3.83 (1H, q, J=6.9 Hz), 4.22 (1H, d, J=7.8 Hz), 4.30 (1H, d, J=7.2 Hz), 4.47 (2H, s), 4.85 (1H, s), 5.06 (1H, dd, J=2.4 and 10.2 Hz), 7.07 (1H, br t, J=6.9 Hz), 7.32 (1H, dt, J=1.2 and 7.8 Hz), 7.43 (1H, dt, J=1.2 and 7.8 Hz), 7.82 (1H, d, J=7.8 Hz), 7.95 (1H, d, J=7.8 Hz); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.2, 12.9, 14.3, 15.3, 15.5, 18.9, 19.9, 21.1, 22.3, 26.4, 28.2, 29.1, 31.5, 33.2, 38.0, 38.3, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.3, 72.9, 76.1, 78.4, 78.6, 82.3, 84.6, 103.7, 121.5, 122.5, 124.5, 125.7, 135.2, 153.2, 153.8, 167.6, 169.2, 170.4, 171.1, 203.9.

Compound **7g**

MS (FAB): 855^+ ($M+H^+$). HR-MS (FAB): calcd for $C_{45}H_{67}N_4O_{12}$ 855.4755 found 855.4749; IR (KBr): 3433, 2973, 2937, 2878, 2784, 1809, 1751, 1716, 1672, 1594, 1569, 1534, 1501, 1455, 1380, 1322, 1305, 1284, 1257, 1233, 1219, 1167, 1142, 1109, 1079, 1048, 1004 (cm^{-1}); ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.81 (3H, t, J=7.2 Hz), 1.01 (3H, d, J=7.2 Hz), 1.23 (3H, d, J=5.7 Hz), 1.26 (3H, d, J=6.6 Hz), 1.28 (3H, d, J=7.5 Hz), 1.37 (3H, d, J=7.2 Hz), 1.39 (3H, s), 1.55 (3H, s), 1.20～2.06 (8H, m), 2.26 (6H, s), 2.44 (1H, m), 2.56 (1H, q, J=6.9 Hz), 2.70 (3H, s), 2.86 (2H, t, J=7.8 Hz), 3.01 (1H, quintet, J=7.8 Hz), 3.14～3.75 (6H, m), 3.83 (1H, q, J=6.9 Hz), 4.22 (1H, d, J=8.1 Hz), 4.29 (1H, d, J=7.5 Hz), 4.45 (2H, s), 4.83 (1H, s), 4.97 (1H, dd, J=2.7 and 10.2 Hz), 7.07 (1H, br t, J=5.7 Hz), 7.35 (1H, dd, J=4.2 and 8.1 Hz), 7.60 (1H, dd, J=2.1 and 8.7 Hz), 7.65 (1H, s), 8.01 (1H, d, J=8.4 Hz), 8.13 (1H, dd, J=1.2 and 8.1 Hz), 8.84 (1H, br s); ^{13}C-NMR ($CDCl_3$) δ (ppm): 10.1, 12.9, 14.3, 15.3, 15.6, 18.8, 19.9, 21.1, 22.2, 26.3, 28.2, 30.6, 33.1, 38.0, 38.9, 40.2, 47.6, 49.8, 51.0, 65.8, 69.5, 70.3, 73.0, 76.0, 78.4, 78.6, 82.4, 84.6, 103.8, 120.9, 126.2, 128.3, 129.2, 131.0, 135.8, 140.1, 147.1, 149.5, 153.8, 167.6, 169.3, 170.4, 203.9.

Preparation of Compound 10d

To a solution of *N*-Boc-propargylamine (2.48 g, 16 mmol) in CH_3CN (32 ml) were successively added NEt_3 (2.22 ml, 16 mmol), CuI (61 mg, 0.32 mmol), 2-iodo-thiophene (0.9 ml, 8 mmol) and $Cl_2Pd(PPh_3)_2$ (112 mg, 0.16 mmol). The reaction mixture was stirred at room temperature for 0.5 hour. The mixture was diluted with H_2O and extracted with AcOEt. The resultant residue was purified by column chromatography on silicagel (toluene/AcOEt=15/1～10/1) to give 1.9 g of compound **8d** (99%).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.47 (9H, s), 4.17 (2H, d, J=3.9 Hz), 4.77 (1H, br s), 6.96 (1H, dd, J=3.6 and 5.1 Hz), 7.18 (1H, dd, J=0.9 and 3.6 Hz), 7.23 (1H, dd, J=0.9 and 5.1 Hz).

Compound **8d** (593 mg, 2.5 mmol) was dissolved in EtOH (8 ml) and AcOEt (8 ml). To this solution was added 5% Pd/C (100 mg) with stirring at room temperature under H_2 atmosphere for 1 hour. The mixture was filtered and concentrated and dissolved in EtOH (8 ml) and AcOEt (8 ml). To this solution was added again 5% Pd/C (100 mg) with stirring at room temperature under H_2 atmosphere for one more hour. The mixture was filtered and concentrated and 603 mg of compound **9d** was obtained (99%).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.45 (9H, s), 1.81 (2H, m), 2.67 (2H, t, J=7.5 Hz), 3.16 (1H, m), 4.55 (1H, br s), 6.92～6.96 (2H, m), 7.25 (1H, dd, J=3.0 and 5.1 Hz).

Compound **9d** (350 mg, 1.45 mmol) was dissolved with CH_2Cl_2 (3.5 ml) and stirred on an ice-water bath. To this solution was added CF_3CO_2H (1.8 ml), and the reaction mixture was stirred for 1 hour and concentrated *in vacuo*. The resultant residue was quenched with diluted aqueous NaOH and extracted with AcOEt. The aqueous layer was extracted with AcOEt, and the combined organic layer was

dried over $MgSO_4$, filtered and concentrated *in vacuo*. Finally, 205 mg of compound **10d** was obtained (86%).

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.74～1.84 (2H, m), 2.68 (2H, t, J=7.5 Hz), 2.74 (2H, t, J=7.2 Hz), 6.94 (1H, br s), 6.95 (1H, br s), 7.24 (1H, m)

Preparation of Compound 10e and 10g

Compound **10e** and **10g** were prepared by the same procedure described for the synthesis of **10d** with 2-bromo-thiazple and 6-bromo-quinoline, respectively.

Compound **10e**

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.90～2.00 (2H, m), 2.80 (2H, t, J=6.6 Hz), 3.10 (2H, t, J=7.5 Hz), 7.19 (1H, d, J=3.6 Hz), 7.67 (1H, d, J=3.6 Hz).

Compound **10g**

^{1}H-NMR ($CDCl_3$) δ (ppm): 1.81～1.95 (2H, m), 2.78 (2H, t, J=7.2 Hz), 2.86 (2H, t, J=7.5 Hz), 7.37 (1H, dd, J=4.2 and 8.4 Hz), 7.55～7.60 (1H, m), 7.60 (1H, s), 8.01～8.12 (2H, m), 8.84～8.88 (1H, m).

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