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Total synthesis and structure revision of deacetylravidomycin M

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ABSTRACT

Total synthesis of the unnatural enantiomer of deacetylravidomycin M was accomplished. The key steps include, (1) aryl C-glycosidation of the azido-bearing fucosyl acetate **2** by using catalytic $Sc(OTf)_3$, (2) the [2+2] cycloaddition reaction of alkoxybenzyne bearing an azido sugar to ketene silyl acetal, and (3) the ring expansion reaction of alkoxybenzocyclobutenone. The synthesis revealed that the natural product is not the proposed amine, but the corresponding *N*-oxide.

1. Introduction

The gilvocarcin–ravidomycins[1] constitute a class of antitumor antibiotics, which share a common tetracyclic aromatic nucleus, to which sugars are attached as a *C*-glycoside at the C(4) position (Fig. 1). These compounds have stimulated considerable synthetic interest due to their significant biological activities and also by the synthetic challenges presented by the *C*-glycoside structures linked to the highly functionalized aromatic skeleton. Although many approaches to the aglycon, defucogilvocarcins, have been reported,[2] successful accesses to the glycosylated structures have been limited to our syntheses of gilvocarcin M,[3] gilvocarcin V,[4] and ravidomycin.[5]

While the synthetic route was effective for the gilvocarcins with a neutral sugar, the application to the synthesis of ravidomycin proved less effective, due to the incompatibility of the amino functionality toward the key benzyne–furan cycloaddition.[5] The late-stage modification of the sugar for introducing the amino functionality made inevitable lack of convergency. In addition, the Pd-catalyzed cyclization, another key step to construct the tetracyclic skeleton, was hampered by deactivation of the catalyst by the *tert*-amino functionality.

Recognizing these issues, we decided to explore the alternative, more effective approaches to circumvent these difficulties, including

(1) the aryl C-glycosidation with a nitrogen-containing sugar;
(2) assembly of the tetracyclic structure without resorting to transition-metal catalysis.

The first issue was solved by the finding of $Sc(OTf)_3$ as an efficient catalyst for aryl C-glycosidation, which was applicable to the reaction of an azido-bearing sugar donor.[6] Innovation to the second issue was provided by a strategy that we call *the* [2+2+2] *approach* (Scheme 1), a catalyst-free, three-step access to the key β-phenylnaphthalene structures:[2i,7] The first stage is the [2+2]-cycloaddition of benzyne **I** to olefin **II** to give benzocyclobutene **III**, to which additional two-carbon unit within a styryl group is installed to give **IV**. Finally, sequential pericyclic reactions form dihydronaphthalene **V**. Ideally, release of the molecular strain through the whole process would allow conversion of the starting structure into the target without aid of the catalysts and/or promoters that might be deteriorated by the nitrogen functionality.

To check out the viability of such strategy, we chose as the target deacetylravidomycin M (**1**),[1e] which has inhibitory activity of IL-4 induced CD23 expression in U937 cells without any cytotoxic effect.

We describe herein the synthesis of the proposed structure **1** by exploiting the [2+2+2] strategy, which not only recorded the first total synthesis, but also allowed the structure revision; the dimethylamino function in **1** is the corresponding *N*-oxide.

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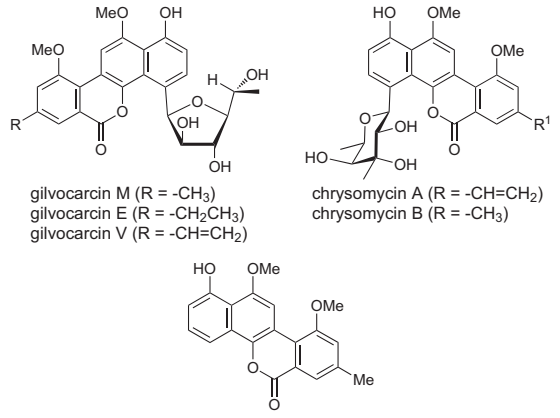


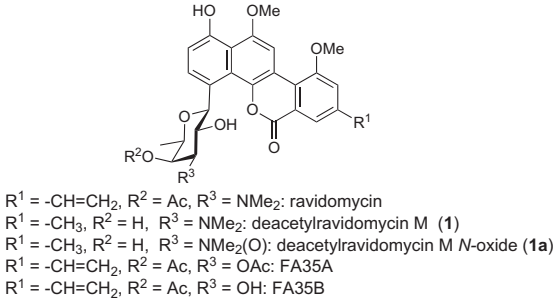
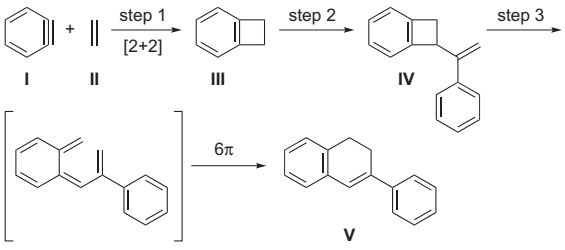


Fig. 1. The gilvocarcin–ravidomycin family of antibiotics.

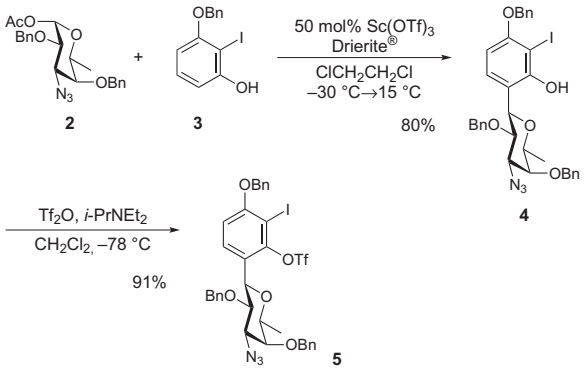


Scheme 1.

2. Results and discussion

2.1. Aryl-C-glycosidation of azido-containing sugar

The synthesis started with the C-glycosidation of the azido-bearing glycosyl acetate **2**,[8] and the reaction with iodophenol **3**[9] was examined. As reported previously,[6a] the reaction by employing $Sc(OTf)_3$ (50 mol %) in the presence of Drierite® (1,2-dichloroethane, −30 °C to 15 °C) afforded β-*C*-glycoside **4** in 80% yield in high selectivity (Scheme 2). The stereostructure of **4** was assigned by extensive ^1H NMR study (Fig. 2; coupling constants, NOE, HMBC). The α-*C*-anomer, produced only in a trace amount (0.5% yield), was easily removed by chromatography. β-*C*-Glycosyl phenol **4**, thus obtained, was converted to triflate **5** (Tf_2O, *i*-Pr_2NEt, CH_2Cl_2, −78 °C, 0.5 h) in 91% yield, ready for the [2+2]-cycloaddition.



Scheme 2.

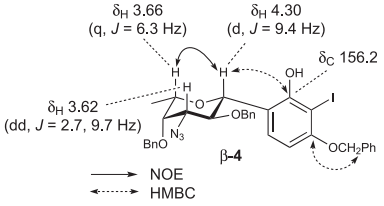


Fig. 2. NMR analysis of β-**4**.

2.2. The [2+2]-cycloaddition; initial attempts

The next step was the [2+2]-cycloaddition of the benzyne species, generated from iodotriflate **5** (*n*-BuLi, −78 °C, THF). Although the initial attempt was made by using ketene silyl acetal (KSA) **6** as the reaction partner, only a trace amount of cycloadduct **7** was obtained (<2% yield, after hydrolytic workup with 46% aqueous HF in CH_3CN). Similar attempts by using various other solvents unfortunately failed to give improved results, which were unexpected in view of our previous success in the non-*C*-glycosyl substrates (see, for example, Eq. 1).[2i] We suspected two potential factors for the failure: (1) presence of the azido function that may competitively react with *n*-BuLi and/or the benzyne species,[10] and (2) presence of the sugar moiety that may pose steric hindrance to the reacting benzyne.

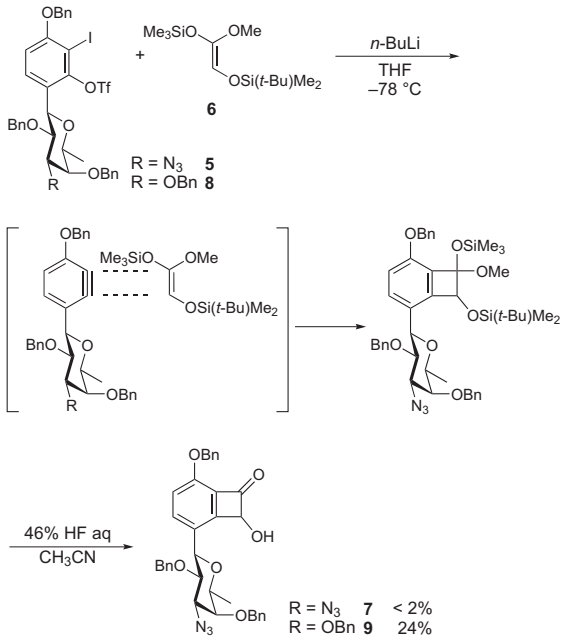
For addressing the first factor, a comparison experiment was carried out for the [2+2]-cycloaddition of iodotriflate **8**,[6a] in which the C(3)-azido group in the sugar was replaced by a benzyloxy group (Scheme 3). Indeed, the yield was slightly improved, suggesting that the azido function interfered the reaction of **5**, at least partially.

We then turned attention to the second factor, the initial orbital interaction of α-alkoxybenzyne (LUMO) and KSA (HOMO). Concerning the α-alkoxybenzyne, the LUMO has a larger coefficient at the side distal from the alkoxy group.[9a,11] Thus, the sugar is located exactly on the approaching vector of the incoming KSA (Fig. 3).

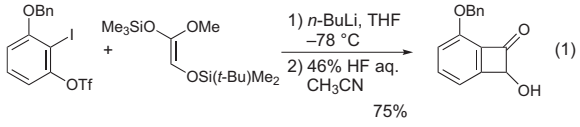
Thus, we decided to carry out a *model study* by subjecting a series of the KSAs[12] with varying steric demands to the reaction of the benzyne species generated from iodotriflate **8** (Table 1). Indeed, KSA **10a** with less steric demand gave an excellent yield of the corresponding [2+2] cycloadduct **11a** (entry 1), although the oxidation level of **11a** was not suitable for the synthetic purpose. As other examples show (entries 2–4), the yields correlated well to the steric demand of the KSAs. Entry 5 shows a promising data obtained by the use of KSA **10e**, in which the *tert*-butyldimethylsilyl (TBDMS) group in **10c** was replaced by a smaller silyl group, trimethylsilyl (TMS).

2.3. Synthesis of benzocyclobutenone with azido sugar

With this clue in mind, we attempted the [2+2]-cycloaddition of the real substrate, i.e., the azido *C*-glycoside **5**. Two points were



Scheme 3.



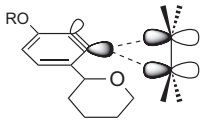


Fig. 3. Primary orbital interaction.

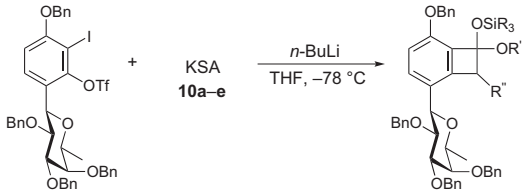
considered, (1) employment of KSA **10e** in excess (5 equiv), and (2) performing the reaction at lower temperature (−98 °C). Under these conditions, we were pleased to find that the requisite adduct **12** was eventually obtained in 74% yield (Table 2).

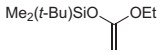
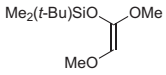
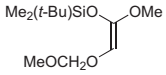
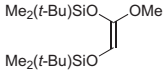
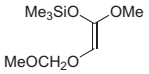
The methoxymethyl group in **12** was removed by acid treatment (12 M HCl, 1,2-dimethoxyethane, 40 °C, 6 h) to give ketol **7**, which was converted to dimethyl acetal **13** [$(MeO)_3CH$, $TsOH\cdot H_2O$, MeOH, room temperature, 17 h] in 91% yield (Scheme 4). Oxidation of the hydroxy group in **13** by using IBX[13] (DMSO, room temperature, 25 h) furnished benzocyclobutenone **14** in 91% yield.

2.4. Construction of the tetracyclic aromatic nucleus

Initial attempts at adding the styryllithium, generated from styryl bromide **15**[14] and *t*-BuLi (THF, −78 °C), to benzocyclobutenone **14** (THF, −78 °C, 1.7 h) afforded a low yield of alcohol **16** (18%) along with the recovery of **14** in 20% yield. Many undefined side products were observed. By changing the solvent to Et_2O, the yield was improved (59%). In order to complete the reaction, we raised the temperature (−78 to −50 °C), where the starting material was

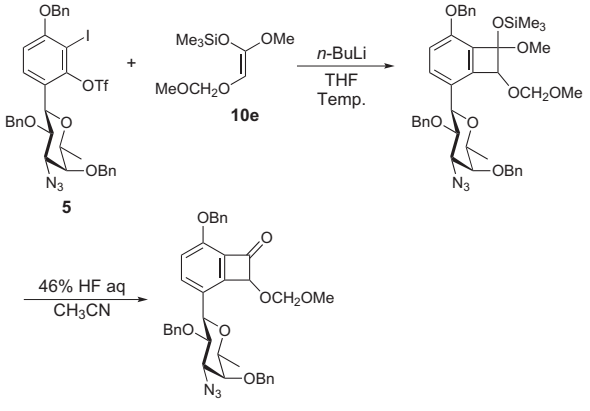
Table 1
Effect of steric demand of KSA on the [2+2]-cycloaddition to benzyne



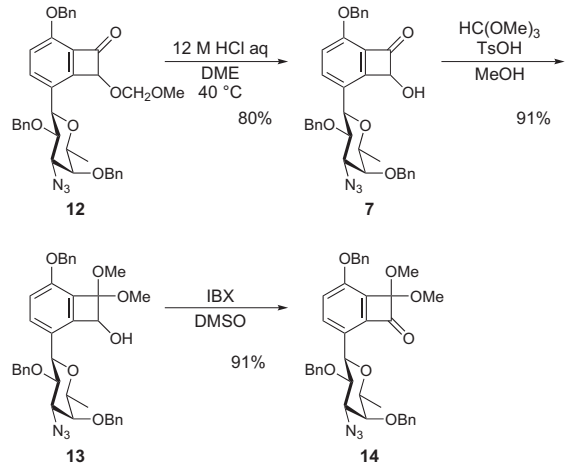
Entry	KSA	Product	Yield/%
1	 **10a**	**11a**	86
2	 **10b**	**11b**	75
3	 **10c**	**11c**	54
4	 **10d**	**11d**	27
5	 **10e**	**11e**	77

completely consumed, though the yield of **16** remained almost the same. In our recent experience, the halogen–lithium exchange reaction of alkenyl bromides and *t*-BuLi tends to proceed more cleanly by employing the 1/1 molar ratio of alkenyl bromide and *t*-BuLi, rather than the standard 1/2 ratio.[15] Much cleaner reaction indeed occurred by employing a lesser amount of *t*-BuLi (1.2 equiv to bromide **15**), giving alcohol **16** in high yield (Scheme 5).

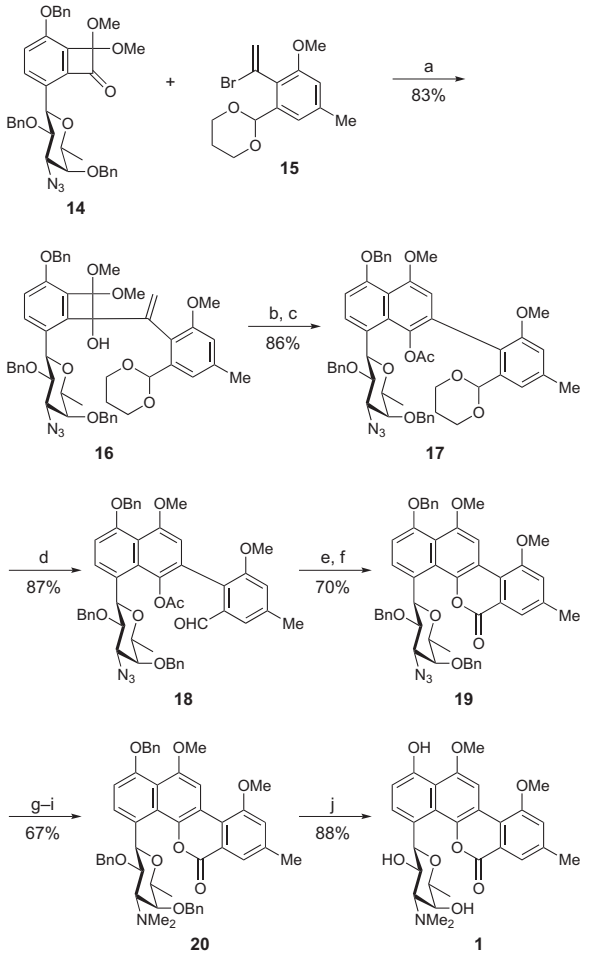
Table 2
[2+2]-Cycloaddition of KSA **10e** to the benzyne generated from **5**



Entry	**10e**/equiv	Temp/°C	Yield/%
1	2	−78	47
2	5	−78	60
3	5	−98	74



Scheme 4.



Scheme 5. Reagents and conditions: (a) **15**, *t*-BuLi (1.2 equiv of **15**), Et_2O, −78 °C, 10 min; then **14**, −78 °C→−50 °C, 100 min; (b) toluene, reflux, 7 h; (c) Ac_2O, DMAP, pyridine, rt, 17 h; (d) 80% AcOH, 40 °C, 1 h; (e) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, acetone, H_2O, rt, 20 min; (f) LiAlH(O*t*-Bu)$_3$, THF, 70 °C, 30 h; then 2 M HCl aq, 0 °C; (g) PMe_3, toluene, rt, 1.7 h; (h) $(HCHO)_n$, CH_2Cl_2, rt, 3 h; then H_2O, THF, rt, 2 h; (i) HCHO aq, CH_3CN, rt, 30 min; then $NaBH_3CN$, AcOH, rt, 15 h; (j) H_2, Pd-black, 2 M HCl aq, MeOH, rt, 53 h.

With substrate **16** in hand, the ring expansion reaction was examined. We were pleased to find that the desired phenylnaphthalene **17** was obtained in excellent yield by heating of alcohol **16** in degassed toluene at 110 °C for 7 h followed by acetylation (86%, two steps). Acetal **17** was hydrolyzed by treatment with 80% acetic acid (40 °C, 1 h) to give aldehyde **18** in 87% yield as a mixture of atropisomers, which were partially separated by silica-gel chromatography. These atropisomers converged to a single lactone **19**, as described in the following.

After aldehyde **18** was oxidized to the corresponding carboxylic acid, removal of the acetyl group was examined. However, the acetate was resistant to hydrolysis under basic/acidic conditions. After considerable experimentation, we found that the acetate could be removed by reduction: after oxidation of aldehyde **18** ($NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, acetone, room temperature, 20 min), the acetyl group was removed by treatment with LiAlH(O*t*-Bu)$_3$ (THF, 70 °C, 30 h), and acidification (2 M HCl, 0 °C) gave lactone **19** in 70% yield. Next, the azido group in **19** was converted into the corresponding primary amine in one-pot through formation of the iminophosphorane (Me_3P, toluene, room temperature, 1.7 h) and subsequent reaction with paraformaldehyde (CH_2Cl_2, room temperature, 3 h) followed by hydrolysis (H_2O, THF, room temperature, 2 h),[16,17] which was then subjected to reductive dimethylation (HCHO aqueous $NaBH_3CN$, AcOH, CH_3CN, room temperature) to give dimethylamine **20** in 67% yield.

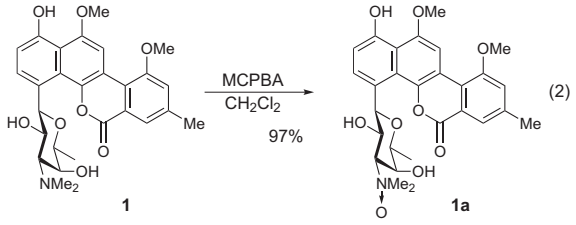
Finally, hydrogenolysis of **20** (H_2, Pd-black, 2 M HCl, MeOH, room temperature, 53 h) afforded the targeted structure **1** in 88% yield.

However, the ^{1}H NMR spectrum of the synthetic material did not coincide with the reported data of the natural product. Significant inconsistency was observed for the peaks around the dimethylamino group (H-2′, H-3′, 3′-NCH_3) (Table 3). Signals of the synthetic material appeared at higher fields than those of the natural product. At this stage, we noticed the possible misassignment of the reported MS data;[18] the parent peak is *m*/*z* 526 rather than *m*/*z* 510, suggesting that the NMe_2(O) function, rather than the NMe_2 group, may be installed on the sugar. Indeed, treatment of **1** with *m*-CPBA (CH_2Cl_2, room temperature, 0.5 h, quant) gave the corresponding *N*-oxide **1a** (Eq. 2), whose spectroscopic data was identical with those of the natural product. The sign of $[\alpha]_D$ of **1a** ($[\alpha]_D^{26}$ +45, *c* 0.36, $CHCl_3$/MeOH=1/1) was opposite to that of the corresponding natural product (lit. $[\alpha]_D^{22}$ −22, *c* 0.3, $CHCl_3$/MeOH=1/1). Thus, the absolute stereochemistry of the natural product was proven to be enantiomeric to the synthetic one.

Table 3
^{1}H-NMR spectra of the reported natural product, synthetic **1**, and *N*-oxide **1a**.[a]

	Reported[1e]	Synthetic **1**	Synthetic **1a**
1-OH	9.85 (1H, br s)	9.85 (1H, br s)	9.84 (1H, br s)
H-2	6.97 (1H, d, *J*=8.3 Hz)	6.97 (1H, d, *J*=8.4 Hz)	6.95 (1H, d, *J*=8.4 Hz)
H-3	7.85 (1H, d, *J*=8.3 Hz)	7.84 (1H, d, *J*=8.4 Hz)	7.84 (1H, d, *J*=8.4 Hz)
H-7	7.74 (1H, d, *J*=1.5 Hz)	7.79 (1H, br s)	7.74 (1H, br s)
H-9	7.44 (1H, d, *J*=1.5 Hz)	7.52 (1H, br s)	7.46 (1H, br s)
10-OCH_3	4.063 (3H, s)	4.11 (3H, s)	4.07 (3H, s)
H-11	8.43 (1H, s)	8.50 (1H, s)	8.45 (1H, s)
12-OCH_3	4.077 (3H, s)	4.12 (3H, s)	4.08 (3H, s)
H-13	2.47 (3H, s)	2.502 (3H, s)	2.48 (3H, s)
H-1′	5.66 (1H, d, *J*=8.8 Hz)	5.67 (1H, d, *J*=9.0 Hz)	5.65 (1H, d, *J*=8.9 Hz)
H-2′	*4.60* (1H, dd, *J*=10.0, 8.8 Hz)	*4.15* (1H, dd, *J*=9.0, 9.0 Hz)	*4.58* (1H, dd, *J*=10.4, 8.9 Hz)
H-3′	*3.50* (1H, dd, *J*=10.0, 2.5 Hz)	*2.62* (1H, br d, *J*=9.0 Hz)	*3.47* (1H, dd, *J*=10.4, 2.7 Hz)
3′-*NCH_3*	*3.35* (3H, s)	*2.504* (6H, s)	*3.33* (3H, s)
3′-*NCH_3*	*3.20* (3H, s)		*3.18* (3H, s)
H-4′	4.06 (1H, d, *J*=2.5 Hz)	3.86–3.85 (1H, m)	4.06 (1H, d, *J*=2.7 Hz)
H-5′	4.13 (1H, q, *J*=6.5 Hz)	4.01 (1H, q, *J*=6.4 Hz)	4.12 (1H, q, *J*=6.4 Hz)
H-6′	1.02 (3H, d, *J*=6.5 Hz)	1.01 (3H, d, *J*=6.4 Hz)	1.00 (3H, d, *J*=6.4 Hz)

[a] Measured in DMSO-d_6.



3. Conclusion

The first total synthesis of deacetylravidomycin M was accomplished via the [2+2+2] approach, thereby revising the natural product structure.

4. Experimental

4.1. General

All reactions dealing with air- and moisture-sensitive compounds were conducted under an atmosphere of argon. Dichloromethane and dichloroethane were distilled successively from P_2O_5 and CaH_2 and stored over MS 4 Å. Commercially available dehydrated solvents, tetrahydrofuran (THF), and diethyl ether (Et_2O), were used. All reagents were used as obtained from commercial sources. For thin-layer chromatography (TLC) analysis, Merck precoated plates (silica-gel 60 F_{254}, Art 5715, 0.25 mm) were used. Merck Kieselgel 60 (70–230 mesh ASTM) was used for flash column chromatography. Silica-gel preparative TLC (PTLC) was performed on Merck Kieselgel 60 F_{254} (Art. 7747).

Melting point (mp) determinations were performed by using Yanaco MP-S3 and MP-500V instruments and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were measured on JEOL JNM AL-400 and JEOL JNM Lamda-400 spectrometers. Chemical shifts are expressed in parts per million downfield from internal tetramethylsilane (d=0). Infrared (IR) spectra were recorded on a Horiba FT-710 spectrometer. Optical rotations ($[\alpha]_D$) were measured on a Jasco DIP-1000 polarimeter. Elemental analyses were recorded on a Perkin–Elmer PE2400 Series II CHNS/O Analyzer.

*4.1.1. C-Glycosyl phenol (**4**).* To a stirred suspension mixture of $Sc(OTf)_3$ (1.28 g, 2.60 mmol), powered Drierite® (15 g), and phenol **3** (2.54 g, 7.79 mmol) in 1,2-dichloroethane (30 mL) was added acetate **2** (2.14 g, 5.19 mmol) in 1,2-dichloroethane (25 mL) −30 °C. After the temperature was gradually raised to 0 °C during 1.5 h, stirring was continued for 1 h at 0 °C, and then 2.5 h at 15 °C. The mixture was poured into satd aqueous $NaHCO_3$ solution at 0 °C. After filtration through a Celite pad, the products were extracted with CH_2Cl_2 (3×), and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=5/1) afforded *C*-glycoside **β-4** as colorless crystals (2.84 g, 80%) and the mixture including **α-4**, which was purified by silica-gel preparative TLC (toluene, then hexane/acetone=6/1) to afford **α-4** (16 mg, 0.5%) as a colorless oil. Compound **β-4**: R_f 0.45 (hexane/CH_2Cl_2/acetone=4/1/1); mp 123–124 °C (EtOH); $[\alpha]_D^{25}$ +121 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 7.52–7.50 (m, 2H), 7.50–7.23 (m, 11H), 7.05–7.03 (m, 3H), 6.41 (d, 1H, J=8.2 Hz), 5.21 (s, 2H), 4.99 (d, 1H, J=11.8 Hz), 4.72 (d, 1H, J=11.8 Hz), 4.38 (d, 1H, J=9.7 Hz), 4.30 (d, 1H, J=9.4 Hz), 4.08 (dd, 1H, J=9.4, 9.7 Hz), 3.69 (d, 1H, J=9.7 Hz), 3.69–3.65 (m, 2H), 3.62 (dd, 1H, J=2.7, 9.7 Hz), 1.18 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.8, 156.2, 137.6, 136.5, 130.0, 128.7, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 126.9, 116.6, 104.0, 81.9, 78.7, 77.4, 77.0, 75.3, 75.0, 70.9, 67.0, 17.1; IR (KBr) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{33}H_{32}IN_3O_5$: C, 58.50; H, 4.76; N, 6.20. Found: C, 58.23; H 4.54; N, 6.18. Compound **α-4**: R_f 0.38 (toluene); $[\alpha]_D^{28}$ −24 (*c* 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (s, 1H), 7.52–7.50 (m, 2H), 7.41–7.23 (m, 12H), 7.10–7.08 (m, 2H), 6.36 (d, 1H, J=8.7 Hz), 5.16 (s, 2H), 5.13 (d, 1H, J=2.9 Hz), 4.73 (d, 1H, J=11.6 Hz), 4.62 (d, 1H, J=11.6 Hz), 4.43 (d, 1H, J=11.5 Hz), 4.34 (d, 1H, J=11.5 Hz), 4.13–4.09 (m, 1H), 4.04 (dd, 1H, J=3.4, 3.9 Hz), 3.97 (dd, 1H, J=3.9, 4.1 Hz), 3.86 (dd, 1H, J=2.9, 3.4 Hz), 1.39 (d, 3H, J=6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 156.4, 137.5, 136.8, 136.6, 128.7, 128.50, 128.49, 128.4, 128.1, 128.00, 127.98, 127.9, 127.8, 126.9, 115.3, 103.7, 78.5, 77.6, 74.7, 73.21, 73.19, 70.8, 70.5, 70.4, 59.8, 13.9; IR (neat) 2110 (N_3) cm^{-1}. Anal. Calcd for $C_{33}H_{32}IN_3O_5$: C, 58.50; H, 4.76; N, 6.20. Found: C, 58.78; H 4.79; N, 5.90.

*4.1.2. Triflate (**5**).* To a stirred solution of phenol **β-4** (5.01 g, 7.40 mmol) and *i*-Pr_2NEt (2.6 mL, 15 mmol) in CH_2Cl_2 (70 mL) was slowly added Tf_2O (1.85 mL, 11.0 mmol) at −78 °C. After stirring for 0.5 h, the mixture was poured into satd aqueous $NaHCO_3$ solution at 0 °C. The products were extracted with EtOAc (3x), and the combined organic extracts were washed with brine, 2 M aqueous HCl solution (x2), brine, sat. aq $NaHCO_3$ solution and brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=6/1) afforded triflate **5** as white amorphous solids (5.45 g, 91%): R_f 0.45 (hexane/EtOAc=4/1); mp<30 °C; $[\alpha]_D^{28}$ +36 (*c* 0.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, 1H, J=8.7 Hz), 7.48–7.28 (m, 10H), 7.25–7.17 (m, 3H), 6.96–6.93 (m, 2H), 6.82 (d, 1H, J=8.7 Hz), 5.18 (s, 2H), 4.96 (d, 1H, J=11.1 Hz), 4.67 (d, 1H, J=11.1 Hz), 4.60 (d, 1H, J=9.2 Hz), 4.42 (d, 1H, J=10.6 Hz), 3.80 (dd, 1H, J=9.2, 9.7 Hz), 3.77 (d, 1H, J=10.6 Hz), 3.69 (q, 1H, J=6.3 Hz), 3.67 (br d, 1H, J=2.9 Hz), 3.63 (dd, 1H, J=2.9, 9.7 Hz), 1.23 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.0, 148.2, 138.0, 136.9, 135.5, 130.2, 128.6, 128.3, 128.23, 128.19, 128.17, 128.1, 127.8, 127.7, 127.0, 126.8, 118.6 (q, J_{C-F}=321 Hz), 112.4, 83.9, 79.2, 78.7, 75.64, 75.59, 75.2, 74.4, 71.5, 67.5, 17.0; IR (KBr) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{34}H_{31}F_3IN_3O_7S$: C, 50.44; H, 3.86; N, 5.19; S, 3.96. Found: C, 50.15; H 4.10; N, 4.96; S, 4.17.

*4.1.3. Ketene silyl acetal (**10e**).* To a stirred mixture of hexamethyldisilazane (4.72 g, 29.2 mmol) in THF (18 mL) was slowly added *n*-BuLi (1.58 M solution in hexane, 17 mL, 27 mmol) at 0 °C. After 15 min, the mixture was cooled at −78 °C, and methyl 2-(methoxymethoxy)acetate (2.99 g, 22.4 mmol) in THF (24 mL) and trimethylsilyl chloride (2.90 g. 43.5 mmol) in hexane (5 mL) were added at −78 °C. After gradual warming to room temperature, stirring was continued for 12 h. The mixture was concentrated under Ar and treated with pentane. After filtration under Ar, the filtrate was concentrated and purified by bulb-to-bulb distillation [70 °C (oven temp)/9 mmHg] to afford KSA **10e** (2.18 g, 47%) as a colorless oil: ^{1}H NMR (400 Hz, $CDCl_3$) δ 5.47 (s, 1H), 4.69 (s, 2H), 3.49 (s, 3H), 3.42 (s, 3H), 0.24 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.5, 107.2, 97.5, 56.0, 55.8, 0.54.

*4.1.4. Benzocyclobutenone (**12**).* To a stirred mixture of triflate **5** (723 mg, 0.894 mmol) and KSA **10e** (919 mg, 4.45 mmol) in THF (23 mL) was slowly added *n*-BuLi (0.78 M solution in hexane, 1.6 mL, 1.3 mmol) at −98 °C. After stirring for 10 min, the reaction was quenched by adding pH 7 phosphate buffer. The mixture was extracted with Et_2O (3×), and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration and removal of the solvents in vacuo, the residue was dissolved in CH_3CN (3.0 mL) and 46% aqueous HF solution (0.25 mL) was added at 0 °C. After stirring for 1.5 h, the mixture was treated with satd aqueous KF solution, and the products were extracted with Et_2O (3×). The combined organic extracts were washed with brine, sat. aq $NaHCO_3$ solution, brine and dried over Na_2SO_4. After filtration, removal of the

solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=5/1, then 4/1) afforded a mixture of the diastereomers of benzocyclobutenone **12** (423 mg, 74%, diastereomer ratio=2.9/1) as a colorless oil. This mixture of diastereomers was used for the next step without separation, while the diastereomers could be partially separated by silica-gel column chromatography. Compound **12a** (major isomer): R_f 0.37 (hexane/EtOAc=4/1); $[\alpha]_D^{29}$ +118 (*c* 1.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.19 (m, 14H), 7.04–7.01 (m, 2H), 6.96 (d, 1H, *J*=8.5 Hz), 5.51 (d, 1H, *J*=12.3 Hz), 5.50 (s, 1H), 5.45 (d, 1H, *J*=12.3 Hz), 4.90 (d, 1H, *J*=10.1 Hz), 4.73 (d, 1H, *J*=7.0 Hz), 4.59 (d, 1H, *J*=10.1 Hz), 4.47 (d, 1H, *J*=10.2 Hz), 4.24 (d, 1H, *J*=9.4 Hz), 4.14 (d, 1H, *J*=7.0 Hz), 4.01 (dd, 1H, *J*=9.4, 9.9 Hz), 3.83 (d, 1H, *J*=10.2 Hz), 3.70–3.66 (m, 2H), 3.60 (dd, 1H, *J*=3.1, 9.9 Hz), 3.31 (s, 3H), 1.26 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.2, 153.4, 152.8, 137.8, 137.6, 137.1, 136.2, 133.0, 129.1, 128.5, 128.44, 128.37, 128.3, 128.2, 128.1, 127.9, 127.8, 118.3, 97.2, 90.0, 80.3, 79.1, 78.9, 76.2, 75.2, 74.8, 74.1, 67.3, 55.4, 17.0; IR (neat) 2100 (N_3), 1760 (CO) cm^{-1}. Anal. Calcd for $C_{37}H_{37}N_3O_7$: C, 69.91; H, 5.87; N, 6.61. Found: C, 69.62; H 5.83; N, 6.32. Compound **12b** (minor isomer): R_f 0.31 (hexane/EtOAc=4/1); $[\alpha]_D^{28}$ +80 (*c* 0.65, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, 1H, *J*=8.5 Hz), 7.41–7.29 (m, 10H), 7.23–7.15 (m, 3H), 7.03–7.01 (m, 2H), 6.99 (d, 1H, *J*=8.5 Hz), 5.56 (s, 1H), 5.51 (d, 1H, *J*=12.1 Hz), 5.46 (d, 1H, *J*=12.1 Hz), 4.97 (d, 1H, *J*=11.1 Hz), 4.72 (d, 1H, *J*=6.8 Hz), 4.68 (d, 1H, *J*=6.8 Hz), 4.65 (d, 1H, *J*=11.1 Hz), 4.47 (d, 1H, *J*=10.4 Hz), 4.30 (d, 1H, *J*=9.2 Hz), 4.00 (d, 1H, *J*=10.4 Hz), 3.94 (dd, 1H, *J*=9.2, 9.7 Hz), 3.70–3.66 (m, 2H), 3.63 (dd, 1H, *J*=2.9, 9.7 Hz), 3.37 (s, 3H), 1.21 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 186.5, 153.1, 153.0, 138.0, 137.9, 136.9, 136.2, 132.9, 128.5, 128.4, 128.3, 128.24, 128.22, 127.88, 127.86, 119.0, 95.7, 88.8, 79.4, 78.8, 77.6, 75.7, 75.1, 74.5, 74.2, 67.7, 55.6, 17.1; IR (neat) 2095 (N_3), 1760 (CO) cm^{-1}. Anal. Calcd for $C_{37}H_{37}N_3O_7$: C, 69.91; H, 5.87; N, 6.61. Found: C, 69.65; H, 5.97; N, 6.40.

*4.1.5. Benzocyclobutenol (**7**).* A mixture of benzocyclobutenone **12** (diastereomer mixture, 2.27 g, 3.57 mmol), DME (190 mL), and 12 M aqueous HCl (19 mL) was stirred at 40 °C for 6 h. The mixture was poured into 2 M aqueous NaOH solution at 0 °C, and the product was extracted with Et_2O (3×). The combined organic extracts were washed with water, brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=3/1) afforded a mixture of diastereomers of benzocyclobutenone **7** (1.68 g, 80%) as amorphous solids. This mixture of diastereomers was used for the next step without separation, while the diastereomers could be partially separated by silica-gel column chromatography. Compound **7a** (major isomer): white amorphous solid; R_f 0.42 (hexane/EtOAc=2/1); mp 33–35 °C; $[\alpha]_D^{28}$ +184 (*c* 1.10, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.26 (m, 14H), 7.17–7.15 (m, 2H), 6.92 (d, 1H, *J*=8.2 Hz), 5.78 (d, 1H, *J*=3.4 Hz), 5.52 (d, 1H, *J*=12.0 Hz), 5.43 (d, 1H, *J*=12.0 Hz), 4.98 (d, 1H, *J*=11.1 Hz), 4.70 (d, 1H, *J*=11.1 Hz), 4.54 (d, 1H, *J*=10.1 Hz), 4.34 (d, 1H, *J*=9.2 Hz), 4.09 (d, 1H, *J*=3.4 Hz), 3.91 (dd, 1H, *J*=9.2, 9.7 Hz), 3.88 (d, 1H, *J*=10.1 Hz), 3.87–3.67 (m, 3H), 1.17 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 185.1, 155.4, 152.9, 136.9, 136.7, 136.2, 136.1, 132.3, 129.0, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.0, 127.9, 117.6, 85.5, 80.8, 79.2, 78.3, 75.8, 75.3, 74.2, 73.8, 67.2, 17.1; IR (KBr) 2102 (N_3), 1763 (CO) cm^{-1}. Anal. Calcd for $C_{35}H_{33}N_3O_6$: C, 71.05; H, 5.62; N, 7.10. Found: C, 70.80; H 5.52; N, 6.84. Compound **7b** (minor isomer): colorless oil; R_f 0.39 (hexane/EtOAc=2/1); $[\alpha]_D^{27}$ +84 (*c* 0.69, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.31 (m, 11H), 7.23–7.15 (m, 3H), 6.96–6.94 (m, 3H), 5.52 (d, 1H, *J*=12.1 Hz), 5.51 (d, 1H, *J*=3.6 Hz), 5.43 (d, 1H, *J*=12.1 Hz), 4.99 (d, 1H, *J*=11.4 Hz), 4.71 (d, 1H, *J*=11.4 Hz), 4.58 (d, 1H, *J*=10.4 Hz), 4.32 (d, 1H, *J*=9.2 Hz), 3.97 (d, 1H, *J*=10.4 Hz), 3.88 (dd, 1H, *J*=9.2, 9.2 Hz), 3.72–3.68 (m, 3H), 3.53 (d, 1H, *J*=3.6 Hz), 1.21 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 184.3, 154.5, 153.2, 137.6, 137.2, 136.3, 136.1, 131.7, 128.8, 128.6, 128.52, 128.48, 128.34, 128.26, 128.2, 128.1, 127.9, 127.5, 118.4, 84.1, 79.6, 78.31, 78.25, 75.6, 75.0, 74.3, 67.6, 17.2; IR (neat) 2101 (N_3), 1764 (CO) cm^{-1}. Anal. Calcd for $C_{35}H_{33}N_3O_6$: C, 71.05; H, 5.62; N, 7.10. Found: C, 71.30; H 5.80; N, 7.06.

*4.1.6. Dimethylacetal (**13**).* A mixture of alcohol **7** (1.66 g, 2.80 mmol), $(CH_3O)_3CH$ (3.1 mL, 28 mmol), and TsOH (50 mg, 0.29 mmol) in MeOH (60 mL) was stirred at room temperature for 18 h. The reaction was quenched by satd aqueous $NaHCO_3$ solution at 0 °C, and the product was extracted with Et_2O (3×). The combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=3/1) afforded mixture of the diastereomers of dimethyl acetal **13** (1.63 g, 91%) as white amorphous solids: R_f 0.37 (hexane/EtOAc=2/1); ^{1}H NMR* (400 MHz, $CDCl_3$) δ 7.48–7.23 (m, 14H), {*7.10–7.07* (m), 7.03–7.01 (m); 2H}, {6.82 (d, *J*=8.5 Hz), *6.79* (d, *J*=8.5 Hz); 1H}, 5.24–5.15 (m, 3H), {4.99 (d, *J*=11.4 Hz), *4.97* (d, *J*=11.6 Hz); 1H}, {*4.71* (d, *J*=11.6 Hz), 4.70 (d, *J*=11.4 Hz); 1H}, {*4.47* (d, *J*=9.9 Hz), 4.42 (d, *J*=9.9 Hz); 1H}, {*4.31* (d, *J*=8.9 Hz), 4.26 (d, *J*=9.2 Hz); 1H}, 3.92–3.84 (m, 1H), {3.78 (d, *J*=9.9 Hz), *3.77* (d, *J*=9.9 Hz); 1H}, 3.67–3.61 (m, 3H), {*3.65* (s), 3.63 (s); 3H}, {*3.54* (d, *J*=5.6 Hz), 3.46 (d, *J*=5.6 Hz); 1H}, {3.50 (s), *3.47* (s); 3H}, {1.22 (d, *J*=6.3 Hz), *1.14* (d, *J*=6.5 Hz); 3H}; ^{13}C NMR** (100 MHz, $CDCl_3$) δ 152.7, 152.4, 146.0, 145.5, 137.9, 137.5, 137.3, 136.8, 136.7, 136.6, 131.1, 130.2, 128.8, 128.7, 128.62, 128.60, 128.56, 128.55, 128.43, 128.36, 128.32, 128.26, 128.1, 128.02, 128.00, 127.94, 127.90, 127.82, 127.78, 127.1, 113.8, 113.6, 106.8, 106.5, 80.5, 79.7, 78.94, 78.88, 78.3, 77.9, 77.5, 75.4, 75.3, 75.0, 74.7, 74.2, 70.64, 70.62, 67.4, 67.2, 52.64, 52.62, 52.1, 17.2; IR (KBr) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{37}H_{39}N_3O_7$: C, 69.68; H, 6.16; N, 6.59. Found: C, 69.45; H 6.33; N, 6.46. (*The signals of corresponding to the major isomer are italicized. **All detected ^{13}C NMR signals are inscribed.)

*4.1.7. Benzocyclobutenone (**14**).* To a stirred solution of acetal **13** (1.63 g, 2.56 mmol) in DMSO (50 mL) was added IBX (1.07 g, 3.82 mmol) at room temperature. After stirring for 25 h, the mixture was treated with 2-propanol (0.20 mL, 2.6 mmol) and further stirred for 1 h. After addition of water and filtration through a Celite pad, the filtrate was extracted with Et_2O (3×), and the combined organic extracts were washed with satd aqueous $NaHCO_3$, brine and dried over $MgSO_4$. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=3/1) afforded ketone **14** (1.48 g, 91%) as white amorphous solids: R_f 0.39 (hexane/EtOAc=4/1); mp 31–33 °C (amorphous); $[\alpha]_D^{29}$ −7.6 (*c* 1.83, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, 1H, *J*=8.5 Hz), 7.48–7.31 (m, 11H), 7.21–7.18 (m, 2H), 7.09 (d, 1H, *J*=8.5 Hz), 7.02–6.99 (m, 2H), 5.25 (s, 2H), 4.99 (d, 1H, *J*=11.5 Hz), 4.69 (d, 1H, *J*=11.5 Hz), 4.61 (d, 1H, *J*=9.2 Hz), 4.43 (d, 1H, *J*=10.5 Hz), 3.90 (dd, 1H, *J*=9.2, 9.4 Hz), 3.83 (d, 1H, *J*=10.5 Hz), 3.74–3.54 (m, 3H), 3.51 (s, 3H), 3.47 (s, 3H), 1.23 (d, 3H, *J*=6.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 154.4, 148.0, 144.5, 138.1, 137.1, 136.1, 132.5, 128.6, 128.3, 128.22, 128.16, 128.1, 128.0, 127.73, 127.66, 127.6, 121.4, 117.2, 79.1, 78.7, 77.2, 75.5, 75.1, 74.3, 71.8, 67.2, 53.7, 53.6, 17.1; IR (KBr) 2100 (N_3), 1770 (CO) cm^{-1}. Anal. Calcd for $C_{37}H_{37}N_3O_6$: C, 69.91; H, 5.87; N, 6.61. Found: C, 69.62; H 5.78; N, 6.36.

4.1.8. Methyl 3-methoxy-5-methyl-2-(2-trimethylsilylethynyl)benzoate. A mixture of triflate **21**[14,19] (21.0 g, 64.0 mmol), $(Ph_3P)_2PdCl_2$ (2.25 g, 3.20 mmol), *n*-Bu_4NI (35.5 g, 96.1 mmol), CuI (1.83 g, 9.63 mmol), and Et_3N (75 mL) in DMF (357 mL) was degassed, and trimethylsilylacetylene (18.5 mL, 131 mmol) was added.[14] After stirring for 18 h at 40 °C, the mixture was poured into ice-colded water, and extracted with Et_2O (3×). The combined organic extracts were washed with water, brine and dried over $MgSO_4$. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=10/1, then 8/1)

afforded the titled compound (14.5 g, 82%) as pale brown powder: R_f 0.47 (hexane/EtOAc=4/1); mp 83–84 °C (hexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (br s, 1H), 6.82 (br s, 1H), 3.90 (s, 3H), 3.88 (s, 3H), 2.37 (s, 3H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.4, 161.2, 139.6, 134.8, 122.5, 114.7, 109.4, 103.5, 98.7, 56.3, 52.0, 21.8, 0.06; IR (KBr) 2158(C≡C), 1711 (CO) cm^{-1}. Anal. Calcd for $C_{15}H_{20}O_3Si$: C, 65.18; H, 7.29. Found: C, 65.30; H 7.43.

*4.1.9. Styrylbenzocyclobutenol (**16**).* To a stirred solution of stylyl bromide **15** (295 mg, 0.942 mmol) in Et_2O (10 mL) was added *t*-BuLi (1.58 M solution in pentane, 0.70 mL, 1.1 mmol) at −78 °C. After stirring for 10 min, ketone **14** (297 mg, 0.467 mmol) in Et_2O (6.0 mL) was added at that temperature. The temperature was gradually raised to −50 °C during 30 min, and then kept for 70 min. The reaction was quenched by adding water-containing THF. The mixture was extracted with Et_2O (3×), and the combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration, removal of the solvents in vacuo and purification by silica-gel preparative TLC (hexane/EtOAc=4/1, then 3/1) afforded styrylbenzocyclobutenol **16** (337 mg, 83%) as white powders: R_f 0.33 (hexane/EtOAc=3/1); mp 79–81 °C; $[\alpha]_D^{26}$ +12.2 (*c* 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.11 (m, 17H), 6.84 (d, 1H, *J*=8.5 Hz), 6.58 (br s, 1H), 6.15 (s, 1H), 5.53 (br s, 1H), 5.25 (br s, 1H), 5.24 (d, 1H, *J*=12.3 Hz), 5.19 (d, 1H, *J*=12.3 Hz), 4.89 (d, 1H, *J*=11.2 Hz), 4.61 (d, 1H, *J*=11.2 Hz), 4.16 (d, 1H, *J*=10.6 Hz), 4.21–4.09 (m, 3H), 4.09 (s, 1H), 3.99 (d, 1H, *J*=10.6 Hz), 3.98–3.87 (m, 2H), 3.73 (dd, 1H, *J*=9.4, 9.9 Hz), 3.68 (3H, s), 3.58 (d, 1H, *J*=2.4 Hz), 3.49 (dd, 1H, *J*=2.4, 9.9 Hz), 3.46 (s, 3H), 3.38 (q, 1H, *J*=6.3 Hz), 3.34 (s, 3H), 2.34 (s, 3H), 2.28–2.17 (m, 1H), 1.39–1.35 (m, 1H), 1.11 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.6, 152.4, 148.0, 142.8, 138.4, 138.2, 138.1, 136.8, 136.7, 131.8, 130.0, 129.0, 128.4, 128.2, 128.01, 127.95, 127.8, 127.6, 127.2, 127.1, 125.9, 122.3, 119.3, 113.9, 111.9, 109.4, 99.9, 89.6, 79.1, 78.8, 77.2, 76.4, 75.3, 74.6, 74.4, 70.4, 67.7, 67.1, 67.0, 55.2, 53.2, 51.6, 26.0, 21.6, 17.1; IR (KBr) 2100 (N_3) cm^{-1}. Anal. Calcd for $C_{51}H_{55}N_3O_{10}$: C, 70.41; H, 6.37; N, 4.83. Found: C, 70.15; H 6.55; N, 4.59.

*4.1.10. Naphthlene (**17**).* A solution of styrylbenzocyclobutenol **16** (504 mg, 0.580 mmol) in toluene (50 mL) was degassed and refluxed at 110 °C for 7 h. After cooling to ambient temperature, the solvent was removed and the residue was dissolved in pyridine (5.0 mL), to which were added DMAP (7.9 mg, 0.065 mmol) and Ac_2O (0.15 mL, 1.6 mmol). The reaction was stirred at room temperature for 17 h, and quenched by adding satd aqueous $NaHCO_3$ solution. The product was extracted with Et_2O (×3), and the combined organic extracts were washed with water, 2 M aqueous HCl solution, water satd aqueous $NaHCO_3$ solution, brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=2/1) afforded naphthalene **17** (441 mg, 86%) as white powder: R_f 0.32 (hexane/EtOAc=2/1); ^{1}H NMR* (400 MHz, $CDCl_3$, 55 °C) δ 7.80–7.75 (m, 1H), 7.61–7.55 (m, 2H), 7.45–7.23 (m, 9H), 7.10–7.05 (m, 3H), 6.98 (d, 1H, *J*=8.2 Hz), 6.87–6.85 (m, 1H), 6.79–6.74 (m, 3H), {5.65 (d, *J*=8.9 Hz), 5.58 (d, *J*=9.2 Hz); 1H}, {5.22 (s), 5.20 (s); 2H}, {5.14 (s), 5.08 (s); 1H}, {4.96 (d, *J*=11.4 Hz), 4.94 (d, *J*=11.4 Hz); 1H}, {4.67 (d, *J*=11.4 Hz), 4.66 (d, *J*=11.4 Hz); 1H}, 4.13–3.98 (m, 4H), {3.90 (s), 3.88 (s); 3H}, 3.75–3.52 (m, 9H), {2.40 (s), 2.39 (s); 3H}, 2.25–2.00 (m, 1H), 1.77 (s, 3H), {1.26–1.23 (m), 1.07–1.04 (m); 1H}, {1.23 (d, *J*=6.3 Hz), 1.22 (d, *J*=6.3 Hz); 3H}; ^{13}C NMR** (100 MHz, $CDCl_3$, 55 °C) δ 168.2, 167.8, 156.8, 156.6, 154.8, 154.7, 139.5, 139.0, 138.9, 138.8, 138.70, 138.66, 138.5, 138.4, 138.3, 137.7, 137.6, 129.9, 129.8, 129.4, 129.2, 128.7, 128.6, 128.34, 128.28, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.63, 127.58, 127.4, 127.20, 127.16, 123.1, 119.5, 119.4, 119.1, 112.8, 112.7, 110.4, 110.2, 109.3, 109.1, 100.30, 100.27, 100.22, 100.20, 80.5, 79.5, 79.3, 78.0, 75.5, 75.2, 74.2, 73.9, 71.9, 68.6, 68.1, 67.21, 67.20, 67.1, 67.0, 56.6, 56.1, 56.0, 25.83, 25.76, 21.69, 21.67, 20.8, 20.7, 17.33, 17.27; IR (KBr) 2100 (N_3), 1766 (CO) cm^{-1}. Anal. Calcd for $C_{52}H_{53}N_3O_{10}$: C, 70.97; H, 6.07; N, 4.78. Found: C, 70.92; H, 6.25; N, 4.49. [Two rotamers (almost 1/1) are observed and the signals are broadened. **All detected ^{13}C NMR signals are inscribed.]

*4.1.11. Aldehyde (**18**).* Naphthalene **17** (401 mg, 0.456 mmol) was dissolved in 80% acetic acid (35 mL) and the resultant solution was stirred at 40 °C. After 1 h, the solution was poured into a mixture of satd aqueous $NaHCO_3$ solution and Et_2O, and extracted with Et_2O (×3). The combined organic extracts were washed with satd aqueous $NaHCO_3$ solution and brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography (hexane/EtOAc=3/1, then 2/1) afforded aldehyde **18** (328 mg, 87%) as white powders. The rotamers were partially separated by silica-gel column chromatography. Compound **18a** (minor): R_f 0.39 (hexane/EtOAc=2/1); ^{1}H NMR* (400 MHz, $CDCl_3$) δ 9.80 (br s, 1H), 7.78 (br d, 1H, *J*=8.7 Hz), 7.61–7.60 (m, 2H), 7.45–7.31 (m, 9H), 7.14–6.80 (m, 8H), 5.60 (d, 1H, *J*=8.9 Hz), 5.23 (s, 2H), 4.92 (d, 1H, *J*=11.1 Hz), 4.64 (d, 1H, *J*=11.1 Hz), 4.03 (dd, 1H, *J*=8.9, 9.4 Hz), 4.00–3.95 (m, 1H), 3.91 (s, 3H), 3.73–3.68 (m, 5H), 3.65 (d, 1H, *J*=2.7 Hz), 3.54 (br d, 1H, *J*=9.4 Hz), 2.46 (s, 3H), 1.76 (s, 3H), 1.22 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.0, 167.9, 157.3, 156.5, 155.1, 139.7, 138.6, 138.3, 137.3, 129.7, 129.3, 128.8, 128.4, 128.3, 128.1, 127.8, 127.7, 127.6, 127.4, 127.1, 125.8, 119.6, 118.8, 109.3, 79.2, 77.8, 77.2, 75.5, 75.1, 74.0, 71.5, 68.1, 56.7, 56.2, 21.7, 21.2, 17.2; IR (KBr) 2100 (N_3), 1763 [C(=O)–O], 1691 [C(=O)–H] cm^{-1}. Anal. Calcd for $C_{49}H_{47}N_3O_9$: C, 71.60; H, 5.76; N, 5.11. Found: C, 71.34; H, 5.47; N, 4.98. Compound **18b** (major): R_f 0.30 (hexane/EtOAc=2/1); ^{1}H NMR* (400 MHz, $CDCl_3$) δ 9.59 (br s, 1H), 7.75 (br s, 1H), 7.61–7.59 (m, 2H), 7.44–7.31 (m, 9H), 7.11–6.70 (m, 8H), 5.61 (br s, 1H), 5.25 (d, 1H, *J*=12.1 Hz), 5.21 (d, 1H, *J*=12.1 Hz), 4.95 (d, 1H, *J*=11.1 Hz), 4.65 (d, 1H, *J*=11.1 Hz), 4.08 (br s, 1H), 4.08–3.65 (m, 4H), 3.90 (s, 3H), 3.77 (s, 3H), 3.65 (d, 1H, *J*=1.9 Hz), 3.57 (br d, 1H, *J*=9.6 Hz), 2.45 (s, 3H), 1.78 (s, 3H), 1.23 (d, 3H, *J*=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 192.9, 168.1, 156.9, 156.4, 155.2, 139.6, 138.3, 137.3, 137.0, 135.0, 129.6, 129.2, 128.8, 128.4, 128.3, 128.1, 127.8, 127.71, 127.65, 127.44, 127.0, 125.78, 119.4, 116.9, 109.3, 79.2, 77.8, 77.2, 75.5, 75.1, 74.0, 71.5, 68.1, 56.7, 56.2, 21.7, 21.2, 17.3; IR (KBr) 2846 (N_3), 2100, 1765 [C(=O)–O], 1693[C(=O)–H] cm^{-1}. Anal. Calcd for $C_{49}H_{47}N_3O_9$: C, 71.60; H, 5.76; N, 5.11. Found: C, 71.32; H, 5.47; N, 4.85. (*The signals are broadened.)

*4.1.12. Lactone (**19**).* To a stirred solution of aldehyde **18** (62.3 mg, 0.0758 mmol) and 2-methyl-2-butene (0.3 mL, 2.8 mmol) in acetone (8.0 mL) were added aqueous solution (4 mL) of $NaClO_2$ (100 mg, 1.15 mmol) and $NaH_2PO_4 \cdot 2H_2O$ (180 mg, 1.15 mmol) at room temperature. After stirring for 20 min at room temperature, the reaction was quenched by adding 1 M aqueous sodium hydrogen sulfite solution at 0 °C, and then 2 M aqueous HCl solution was added. The mixture was extracted with CH_2Cl_2 (×3) and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed in vacuo, and the residue was dissolved in THF (2 mL) and then LiAlH(*t*-OBu)$_3$ (158 mg, 0.632 mmol) was added. After stirring for 30 h at 70 °C, the reaction was quenched by adding 2 M aqueous HCl solution at 0 °C, and mixture was extracted with CH_2Cl_2 (×3). The combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration and removal of the solvents in vacuo, the resultant yellow solids were washed with MeOH to give lactone **19** (37.6 mg, 65%) as yellow powder. Purification of the filtrate by silica-gel preparative TLC (hexane/EtOAc=1/1.2) gave the second crap of **19** (2.9 mg, 5%) as yellow powders: R_f 0.40 (hexane/acetone=3/1); mp 136–137 °C; $[\alpha]_D^{27}$ −210 (*c* 0.31, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.98 (d, 1H, *J*=8.5 Hz), 7.87 (br s, 1H), 7.62–7.60 (m, 2H), 7.51–7.49 (m, 2H), 7.43–7.31 (m, 6H), 7.14 (br s, 1H), 7.11 (d, 1H, *J*=8.5 Hz), 6.89–6.86 (m, 1H), 6.83–6.79 (m, 2H), 6.54–6.51 (m, 2H), 6.41 (d, 1H, *J*=8.7 Hz), 5.26 (d, 1H, *J*=12.1 Hz), 5.22 (d, 1H, *J*=12.1 Hz), 5.01 (d, 1H,

J=11.4 Hz), 4.72 (d, 1H, J=11.4 Hz), 4.35 (d, 1H, J=10.4 Hz), 4.17 (q, 1H, J=6.3 Hz), 4.08 (s, 3H), 3.99 (s, 3H), 3.99 (dd, 1H, J=2.9, 9.7 Hz), 3.92 (dd, 1H, J=8.7, 9.7 Hz), 3.78 (br d, 1H, J=2.9 Hz), 3.53 (d, 1H, J=10.4 Hz), 2.52 (s, 3H), 1.32 (d, 3H, J=6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 157.2, 155.5, 152.9, 142.1, 139.7, 138.4, 137.5, 137.3, 128.4, 128.29, 128.28, 128.1, 127.71, 127.67, 127.5, 127.3, 127.1, 126.8, 125.4, 122.6, 122.24, 122.16, 119.0, 118.1, 114.8, 110.1, 105.5, 81.2, 79.5, 78.3, 75.6, 75.3, 73.9, 71.7, 68.0, 56.9, 56.3, 21.6, 17.3; IR (KBr) 2098 (N_3), 1722 (CO) cm^{-1}. Anal. Calcd for $C_{47}H_{43}N_3O_8$: C, 72.57; H, 5.57; N, 5.40. Found: C, 72.32; H, 5.51; N, 5.14.

*4.1.13. Dimethylamine (**20**).* To a stirred solution of lactone **19** (22.6 mg, 29.1 mmol) in toluene (5.0 mL) was added 1 M toluene solution of PMe_3 (0.15 mL, 0.15 mmol) at room temperature. After stirring for 1.7 h, the solvent was removed in vacuo, and the residue was dissolved in CH_2Cl_2. Paraformaldehyde (11.3 mg, 0.38 mmol) was added, and the mixture was stirred for 3 h. Water-containing THF [water/THF=1/9 (v/v)] was added, and the stirring was continued for 2 h. After addition of water, the mixture was extracted with CH_2Cl_2 (×3), and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, the solvents were removed in vacuo, and the residue was dissolved in CH_3CN (2 mL), and formalin (0.3 mL) was added. After stirring for 0.5 h, acetic acid (0.1 mL) and $NaBH_3CN$ (12.0 mg, 0.19 mmol) were added at room temperature, and the stirring was continued for 15 h. The reaction was quenched by adding satd aqueous $NaHCO_3$ solution at 0 °C. The mixture was extracted with EtOAc (×3), and the combined organic extracts were washed with brine and dried over Na_2SO_4. After filtration, removal of the solvents in vacuo and purification by silica-gel column chromatography ($CHCl_3$/MeOH=30/1) afforded dimethylamine **20** (15.2 mg, 67%) as yellow powder: R_f 0.40 ($CHCl_3$/MeOH=10/1); mp 95–98 °C; $[\alpha]_D^{22}$ −173 (c 1.02, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.05 (d, 1H, J=8.4 Hz), 7.90 (br s, 1H), 7.59 (br d, 2H, J=7.6 Hz), 7.49 (d, 2H, J=7.2 Hz), 7.41–7.36 (m, 4H), 7.33–7.29 (m, 2H), 7.15 (d, 1H, J=8.4 Hz), 7.14 (br s, 1H), 6.82 (br t, 1H, J=7.3 Hz), 6.78–6.74 (m, 2H), 6.51 (d, 2H, J=7.3 Hz), 6.42 (d, 1H, J=8.8 Hz), 5.24 (d, 1H, J=12.4 Hz), 5.22 (d, 1H, J=12.4 Hz), 4.96 (d, 1H, J=10.7 Hz), 4.73 (d, 1H, J=10.7 Hz), 4.22 (d, 1H, J=10.7 Hz), 4.12 (q, 1H, J=6.4 Hz), 4.06 (s, 3H), 4.07–4.03 (m, 1H), 3.94 (s, 3H), 3.90–3.89 (m, 1H), 3.33 (d, 1H, J=10.7 Hz), 3.23–3.18 (m, 1H), 2.64 (s, 6H), 2.52 (s, 3H), 1.36 (d, 3H, J=6.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 157.5, 155.6, 153.1, 142.6, 139.7, 139.2, 138.6, 137.6, 128.6, 128.5, 128.3, 127.8, 127.7, 127.43, 127.42, 127.3, 126.7, 126.4, 125.6, 123.0, 122.6, 122.5, 119.5, 118.5, 114.8, 111.2, 106.1, 83.2, 80.6, 79.3, 76.7, 75.1, 72.2, 71.7, 69.3, 57.2, 56.5, 48.9, 43.8, 21.6, 17.4; IR (KBr) 1718 (CO) cm^{-1}; HRMS (FAB) m/z calcd for $C_{49}H_{50}O_8N$ (MH^+) 780.3473. Found: 780.3505. Anal. Calcd for $C_{49}H_{49}NO_8$: C, 75.46; H, 6.33; N, 1.80. Found: C, 75.19; H, 6.47; N, 1.68.

*4.1.14. Deacetylravidomycin M (**1**).* A suspension of compound **20** (30.8 mg, 39.5 mmol), Pd-black in 2 M aqueous HCl solution (0.4 mL), and MeOH (3.0 mL) was stirred at room temperature under H_2 atmosphere. After stirring for 53 h, reaction mixture was filtrated through a Celite pad, and satd aqueous $NaHCO_3$ solution was added. The mixture was extracted with $CHCl_3$ (×3), and the combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration and removal of the solvents in vacuo, the resultant yellow solids were washed with hexane/EtOAc=20/1 several times on a funnel. Drying in vacuo afforded **1** (17.8 mg, 88%) as yellow powder: R_f 0.56 ($CHCl_3$/MeOH/H_2O=6/4/0.3); mp 215–219 °C (decomp.); $[\alpha]_D^{26}$ +47 (c 0.20, $CHCl_3$); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.85 (br s, 1H), 8.50 (1H, s), 7.84 (d, 1H, J=8.4 Hz), 7.79 (br s, 1H), 7.52 (br s, 1H), 6.97 (d, 1H, J=8.4 Hz), 5.67 (d, 1H, J=9.0 Hz), 4.36 (br s, 1H), 4.15 (dd, 1H, J=9.0, 9.0 Hz), 4.12 (s, 3H), 4.11 (s, 3H), 4.01 (q, 1H, J=6.4 Hz), 3.86–3.85 (m, 1H), 2.62 (br d, 1H, J=9.0 Hz), 2.504 (s, 6H), 2.502 (s, 3H), 1.01 (d, 3H, J=6.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.7, 157.0, 153.5, 151.8, 141.9, 140.5, 129.5, 126.7, 125.0, 121.6, 121.2, 120.9, 119.1, 115.2, 113.5, 111.8, 101.8, 79.5, 75.7, 69.9, 69.3, 66.1, 56.6, 56.3, 41.9, 40.1, 21.1, 17.0; IR (KBr) 1712 (CO) cm^{-1}; HRMS (FAB) m/z calcd for $C_{28}H_{32}O_8N$ (MH^+) 510.2128. Found: 510.2125.

*4.1.15. Deacetylravidomycin M N-oxide (**1a**).* To a stirred solution of deacetylravidomycin M (**1**) (3.4 mg, 6.7 mmol) in CH_2Cl_2 (1.0 mL) was added *m*-CPBA (1.2 mg, 7.0 mmol) at room temperature. After stirring for 0.5 h, purification by column chromatography (Chromatorex NH-DM1020, Fujisilysia Chemical LTD, $CHCl_3$/MeOH=30/1) gave *N*-oxide **1a** (3.4 mg, 97%.) as yellow powders: R_f 0.62 (Chromatorex NH-DM1020; $CHCl_3$/MeOH=10/1); mp 202–204 °C (decomp.); $[\alpha]_D^{22}$ +45 (c 0.36, $CHCl_3$/MeOH=1/1); ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.84 (br s, 1H), 8.45 (s, 1H), 7.84 (d, 1H, J=8.4 Hz), 7.74 (br s, 1H), 7.46 (br s, 1H), 6.95 (d, 1H, J=8.4 Hz), 5.65 (d, 1H, J=8.9 Hz), 4.58 (dd, 1H, J=8.9, 10.4 Hz), 4.12 (q, 1H, J=6.4 Hz), 4.08 (s, 3H), 4.07 (3H, s), 4.06 (br d, 1H, J=2.7 Hz), 3.47 (dd, 1H, J=2.7, 10.4 Hz), 3.33 (s, 3H), 3.18 (3H, s), 2.48 (s, 3H), 1.00 (d, 3H, J=6.4 Hz); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.8, 157.1, 153.7, 151.9, 141.9, 140.6, 129.7, 125.3, 125.2, 121.6, 121.3, 120.9, 119.2, 115.3, 113.7, 111.8, 101.8, 80.3, 79.7, 75.1, 68.0, 66.7, 57.6, 56.6, 56.3, 55.1, 21.1, 16.8; IR (KBr) 1711 (CO) cm^{-1}; HRMS (FAB) m/z calcd for $C_{28}H_{32}O_9N$ (MH^+) 526.2077. Found: 526.2090.

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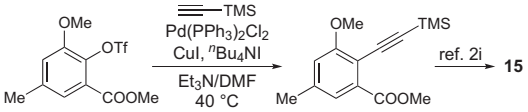

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