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Synthetic Study of Dragmacidin E: Construction of the Core Structure Using Pd-Catalyzed Cascade Cyclization and Rh-Catalyzed Aminoacetoxylation

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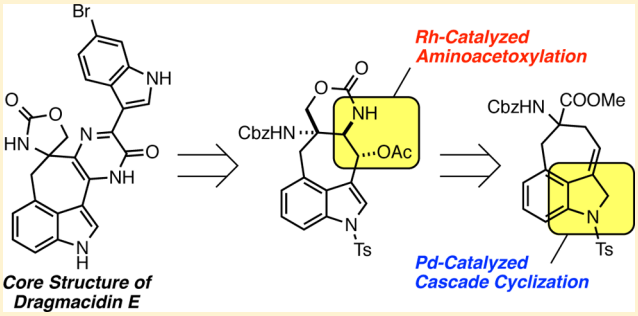
Supporting Information

ABSTRACT: We developed a novel synthetic method of the core structure of dragmacidin E bearing a 7-membered ring-fused bis(indolyl)pyrazinone skeleton. Formation of the 7-membered ring-fused tricyclic indole skeleton was accomplished using a palladium-catalyzed Heck insertion−allylic amination cascade. Vicinal difunctionalization of the 7-membered ring was realized via a rhodium-catalyzed aminoacetoxylation.



Dragmacidin E (**1**) was isolated from an Australian marine sponge, *Spongosorites* sp., by Capon et al. in 1998.[1] The structure features a 7-membered ring-fused tricyclic indole skeleton functionalized with an indolyl pyrazinone motif and two contiguous stereocenters (Figure 1). Because of its unique

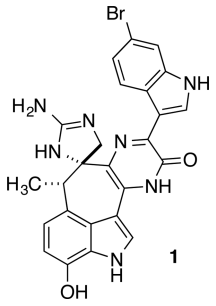
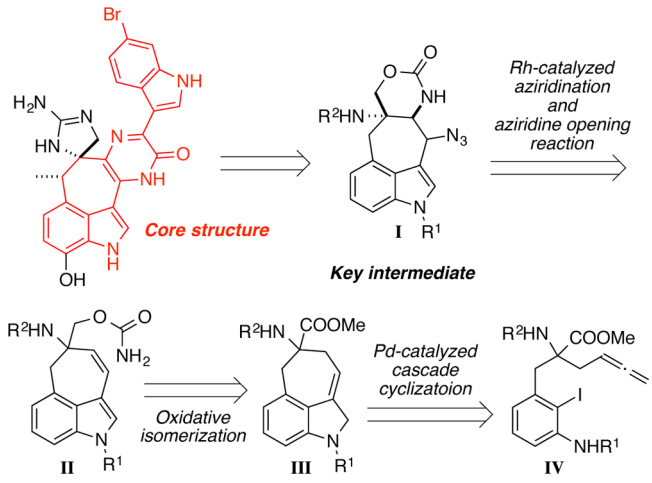


Figure 1. Structure of dragmacidin E (**1**).

structure, dragmacidin E is an attractive target for synthetic organic and medicinal chemists. In addition to several synthetic studies,[2] an example of a total synthesis of racemic dragmacidin E was reported by Feldman et al. in 2011 based on the Witkop photocyclization to construct the 7-membered ring-fused tricyclic indole skeleton.[3] Epimerization of the chiral centers, however, was unavoidable in their synthetic route, and thus a new synthetic strategy for this natural product that is applicable to enantioselective synthesis is desired. It is noteworthy that this natural product exhibits serine-threonine phosphatase inhibitory activity.[1] Dragmacidin E cannot be efficiently obtained from natural sources (0.01% yield from the natural source), however, hampering detailed investigation into its biological activities. This background led us to initiate synthetic studies of this natural product. Herein we report our primary efforts toward the synthesis of dragmacidin E. Construction of the core 7-membered ring-fused bis(indolyl)pyrazinone structure was achieved by palladium-catalyzed cascade cyclization and rhodium-catalyzed aminoacetoxylation as key steps.

Our synthetic plan is outlined in Scheme 1. We first aimed to develop an efficient method for constructing the core structure of dragmacidin E bearing a 7-membered ring-fused bis(indolyl)pyrazinone skeleton. Toward this end, we set

Scheme 1. Synthetic Plan



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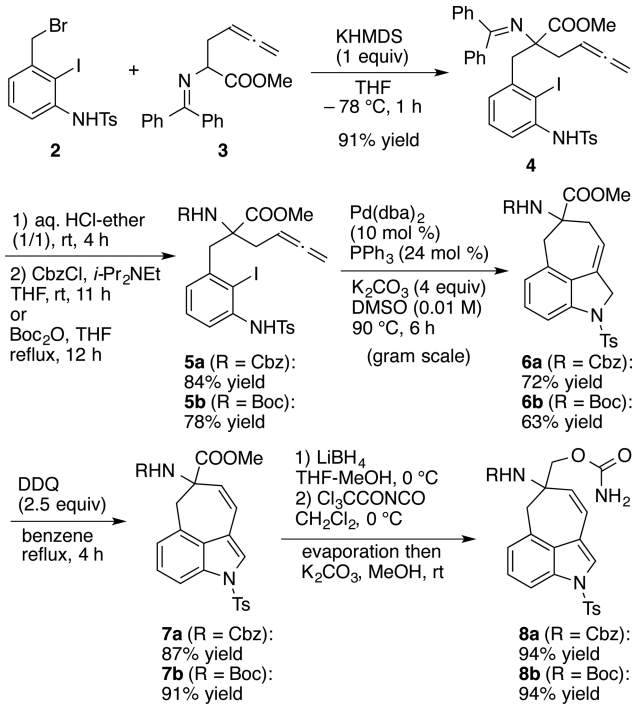
compound **I** as the key intermediate for this study. We envisioned that formation of an aziridine using a rhodium-catalyzed nitrene insertion of **II**, followed by an aziridine opening reaction, would be applicable to the synthesis of **I**. Compound **II** would be accessible via oxidative isomerization of 3-alkylidene indoline derivative **III**, which could be prepared from iodoaniline derivative **IV** using a palladium-catalyzed cascade cyclization involving an intramolecular Heck insertion to an allene and allylic amination sequence that was recently developed in our laboratory.[4]

Our synthesis began with a condensation reaction of known benzyl bromide derivative **2**[4a] with allenyl glycine derivative **3**[5] (Scheme 2). The reaction proceeded using 1 equiv of KHMDS

Scheme 2. Synthesis of Carbamate Derivatives 8a and 8b



in THF at −78 °C to give compound **4** in 91% yield. Hydrolysis of the Shiff base unit followed by protection of the primary amine with a Cbz group afforded compound **5a** in 84% yield. To investigate the compatibility of the protecting group, Boc-protected product **5b** was also prepared in 78% yield. Cascade cyclization of **5a** and **5b** was then performed using 10 mol% of $Pd(dba)_2$, 24 mol% of PPh_3, and 4 equiv of K_2CO_3 in DMSO at 90 °C on a gram scale. The corresponding 7-membered ring-fused 3-alkylidene indoline derivatives **6a** and **6b** were obtained in 72% yield and 63% yield, respectively. Compounds **6a** and **6b** were directly transformed into olefin-conjugated 3,4-fused indole derivatives **7a** and **7b** in high yield by treating with DDQ in refluxed benzene. The olefin on the 7-membered ring can be a useful scaffold for constructing a dihydropyrazinone ring. Subsequent reduction of the methyl ester with $LiBH_4$ in a THF-MeOH mixed solvent,[6] followed by the introduction of a carbamate unit into the alcohol, provided compounds **8a** and **8b** in excellent yield.

A rhodium-catalyzed nitrenoid insertion into alkenes is a highly useful method for synthesizing aziridines.[7] The rhodium-catalyzed nitrenoid insertion combined with a subsequent aziridine opening reaction enables straightforward vicinal difunctionalization of olefins.[8] Thus, compound **8a** was first reacted with 5 mol% of $Rh_2(OAc)_4$, 1.8 equiv of $PhI(OAc)_2$, and 2.3 equiv of MgO in benzene at room temperature to synthesize the corresponding aziridine derivative. Contrary to our expectations, the aziridine adduct was not isolated and acetate derivative **9a** was produced in 40% yield (Table 1, Entry 1). Compound **9a** was formed via an aziridine opening reaction with an acetate nucleophile generated during the formation of rhodium nitrenoid species from the rhodium catalyst and $PhI(OAc)_2$.[9] This finding led us to investigate the rhodium-catalyzed aminoacetoxylation of **8a** in detail.[10] Screening of rhodium catalysts revealed that the $Rh_2(esp)_2$ complex was the most effective catalyst for this transformation and compound **9a** was obtained in 64% yield (Entry 4). The reaction media also affected the reactivity, and we determined that CH_2Cl_2 was the solvent that provided the best chemical yield (71% yield) (Entry 7). Finally, when the reaction was performed using 1 mol% of $Rh_2(esp)_2$ complex at 40 °C, compound **9a** was obtained in 66% yield (61% yield in 509 mg scale) (Entry 10). Similarly, when Boc-protected substrate **8b** was treated with the same reaction conditions, the corresponding product **9b** was obtained in 67% yield (62% yield in 589 mg scale) (Entry 11).

We next examined the introduction of a vicinal diamine unit on the seven-membered ring using **9a** and **9b** (Scheme 3). There are two possible synthetic pathways for this purpose according to the order of processes, including the opening of the 6-membered cyclic carbamate and substitution of the acetate moiety with an azide nucleophile. We first examined the substitution of the acetate in **9a** and **9b** with an azide nucleophile. After removing the acetyl group, the obtained crude residue was reacted with diphenylphosphoryl azide (DPPA) in the presence of DBU.[11] Although the key intermediates **10a** and **10b** were obtained in 36% yield and 63% yield, respectively, both reactions required heating conditions due to low reactivity, probably caused by the steric effect of the 6-membered cyclic carbamate moiety. Compound **10b** was obtained as a crystalline compound. The relative configuration of the three contiguous stereocenters was determined by X-ray crystallography.[12] We thus carried out the opening of the 6-membered cyclic carbamate in **9a** and **9b** prior to the introduction of an azide group. We utilized a general protocol for this transformation based on a Boc protection of the carbamate nitrogen followed by alkaline hydrolysis. When Boc-protected **9b** was used as the substrate, we obtained the expected product **11**, but only in 17% yield. In contrast, when Cbz-protected **9a** was treated under the same reaction conditions, the primary alkoxide generated in the carbamate-opening process sequentially reacted with the Cbz group, providing carbamate derivative **12** bearing a 5- and 7-membered ring-fused spirocyclic molecular framework in 65% yield. Considering the structural similarity to the partial structure of dragmacidin E, we regarded **12** as an ideal model compound for this study and performed further investigations. The secondary alcohol liberated under the reaction conditions of the previous step was successfully transformed into an azide group under mild conditions and compound **13** was obtained in 84% yield.

Construction of the indolyl pyrazinone moiety was then studied (Scheme 4). After reducing the azide in **13** using zinc powder, the resulting amine was coupled with known acid chloride **14**[13] to give compound **15** in 87% yield (2 steps). Deprotection of the tosyl group was subsequently performed under basic conditions, providing compound **16** in 45% yield

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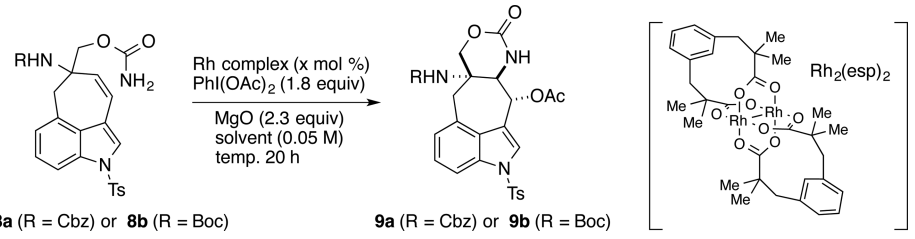
Table 1. Rhodium-Catalyzed Aminoacetoxylation of 8

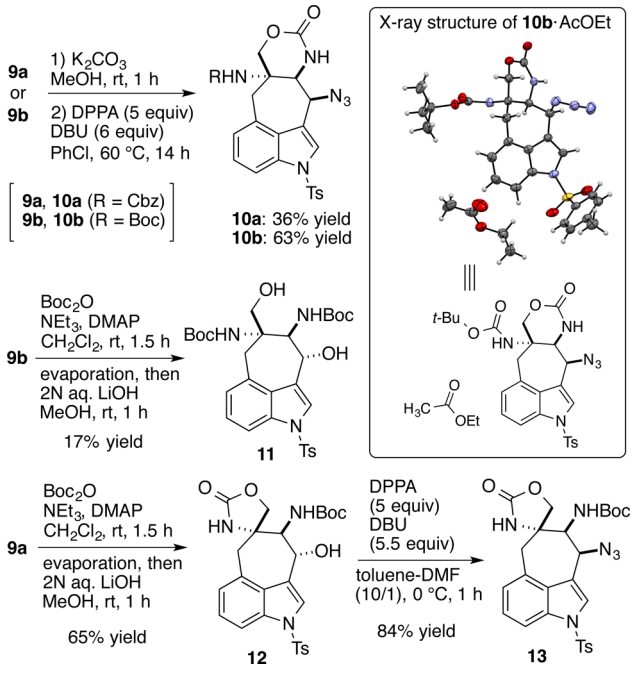


8a (R = Cbz) or **8b** (R = Boc) **9a** (R = Cbz) or **9b** (R = Boc)

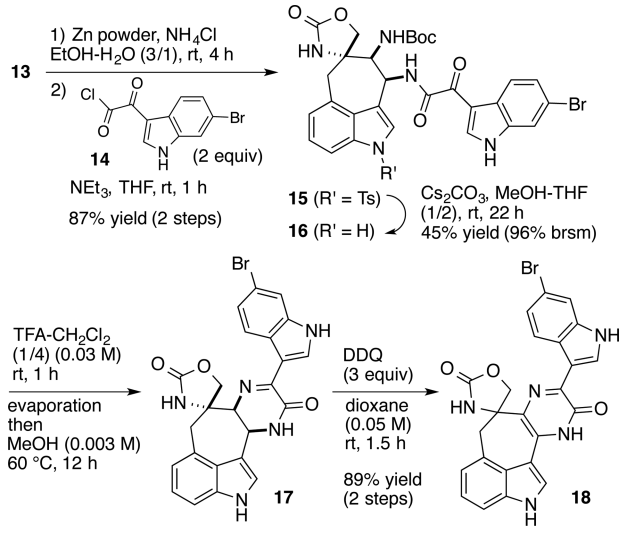
entry	substrate	Rh complex	X mol%	solvent	temp.	product	yield[a]
1	**8a**	$Rh_2(OAc)_4$	5	benzene	rt	**9a**	40%
2	**8a**	$Rh_2(NHCOCF_3)_4$	5	benzene	rt	**9a**	33%
3	**8a**	$Rh_2(O_2CCPh_3)_4$	5	benzene	rt	**9a**	26%
4	**8a**	$Rh_2(esp)_2$	5	benzene	rt	**9a**	64%
5	**8a**	$Rh_2(esp)_2$	5	toluene	rt	**9a**	52%
6	**8a**	$Rh_2(esp)_2$	5	CH_3CN	rt	**9a**	45%
7	**8a**	$Rh_2(esp)_2$	5	CH_2Cl_2	rt	**9a**	71%
8	**8a**	$Rh_2(esp)_2$	2	CH_2Cl_2	rt	**9a**	61%
9	**8a**	$Rh_2(esp)_2$	2	CH_2Cl_2	40 °C	**9a**	62%
10	**8a**	$Rh_2(esp)_2$	1	CH_2Cl_2	40 °C	**9a**	66% (61%)[b]
11	**8b**	$Rh_2(esp)_2$	1	CH_2Cl_2	40 °C	**9b**	67% (62%)[c]

[a]Isolated yield. [b]Reaction was performed in 509 mg scale. [c]Reaction was performed in 589 mg scale.

Scheme 3. Introduction of an Azide Group



Scheme 4. Construction of the 7-Membered Ring-Fused Bis(indolyl)pyrazinone Skeleton



(96% yield based on the recovered starting material). Removal of the Boc group in **16** with TFA, followed by heating the crude residue in MeOH at 60 °C, afforded intermediate **17**. Finally, compound **17** was reacted with DDQ in dioxane to give compound **18** bearing a 7-membered ring-fused bis(indolyl)-pyrazinone skeleton in 89% yield in 2 steps. We examined the transformation of the 5-membered spirocyclic carbamate in **18** into the corresponding guanidine using a known synthetic method.[14] The pyrazinone moiety, however, is reactive under the reaction conditions and the substrate decomposed. This information suggests that a spirocyclic urea framework must be introduced before forming the pyrazinone ring. We are currently working on this new approach.

In conclusion, we successfully developed a novel synthetic method of the core structure of dragmacidin E bearing a 7-membered ring-fused bis(indolyl)pyrazinone skeleton. Formation of the 7-membered ring-fused tricyclic indole skeleton was accomplished using a palladium-catalyzed Heck insertion–allylic amination cascade. Vicinal difunctionalization of the 7-membered ring was realized via a rhodium-catalyzed amino-acetoxylation. After conversion into the carbamate derivative bearing a 5- and 7-membered ring-fused spirocyclic molecular framework, the indolyl pyrazinone moiety was constructed to give the product with the core structure of dragmacidin E.

EXPERIMENTAL SECTION

General Information. Infrared (IR) spectra were recorded on a Fourier transform infrared spectrophotometer, equipped with ATR. NMR spectra were recorded with 400 or 600 MHz spectrometers. Chemical shifts in $CDCl_3$ and DMSO-d_6 were reported downfield

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from TMS (= 0 ppm) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent signal [$CHCl_3$ (77.0 ppm), DMSO (39.5 ppm)] as an internal reference. Positive-ion mass spectra were recorded by electrospray ionization (ESI-TOF). Reactions were carried out in dry solvent. Other reagents were purified by the usual methods.

Compound 2. This compound was prepared using the previously reported procedure.[4a]

Compound 3. This compound was prepared using the reported procedure.[5]

Compound 4. To a stirred solution of **3** (1.80 g, 5.89 mmol) in THF (9.8 mL) was slowly added KHMDS (11.8 mL, 0.5 M in toluene, 5.90 mmol) at −78 °C in a dry ice−acetone bath. The resulting solution was then stirred for 30 min at the same temperature. A THF solution of **2** (1.10 g, 2.35 mmol in 5.0 mL of THF) was added slowly. The resulting mixture was stirred for 30 min at the same temperature, then stirred for an additional 20 min at 0 °C. The reaction mixture was diluted with saturated aq. NH_4Cl solution and AcOEt. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 15/1 to 6/1) to give **4** (1.49 g, 91% yield) as yellow oil. IR (ATR) ν 664, 703, 813, 849, 911, 1091, 1163, 1381, 1444, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H), 2.56 (dt, J = 5.2, 2.4 Hz, 2H), 3.24 (s, 3H), 3.36 (d, J = 15.2 Hz, 1H), 3.48 (d, J = 15.2 Hz, 1H), 4.58 (dt, J = 7.2, 2.4 Hz, 2H), 5.06 (tt, J = 5.2, 7.2 Hz, 1H), 6.97 (d, J = 7.2 Hz, 2H), 7.04 (s, 1H), 7.17 (dd, J = 7.6, 7.6 Hz, 2H), 7.28−7.40 (m, 10H), 7.52 (dd, J = 6.0, 6.0 Hz, 2H), 7.62 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$): δ 21.5, 37.8, 49.8, 51.6, 69.7, 74.4, 85.3, 102.6, 120.4, 127.5 (2C), 127.8 (2C), 127.9 (2C), 127.9, 128.0 (2C), 128.1, 128.2 (2C), 128.5, 128.5 (2C), 130.2, 136.0, 137.0, 137.5, 140.6, 142.0, 144.0, 166.9, 173.4, 210.0; (+)-ESI-HRMS. Calcd for $C_{34}H_{32}IN_2O_4S$ ($M+H^+$): 691.1122; found: 691.1112.

Compound 5a. To a solution of **4** (4.19 g, 6.08 mmol) in Et_2O (60 mL) was added 10% HCl (60 mL), and the resulting mixture was stirred vigorously for 4 h at room temperature. The ether layer was separated, and the aqueous layer was extracted twice with ether to remove benzophenone. The aqueous layer was then stirred with solid $NaHCO_3$ and ether for 15 min. The ether layer was separated and the aqueous layer was extracted with Et_2O. The organic extracts were washed with brine, dried over sodium sulfate. After concentration *in vacuo*, the obtained residue was directly utilized for the next reaction. To a stirred solution of crude product in THF (60 mL) at 0 °C was added *N*-ethyldiisopropylamine (1.2 mL, 7.29 mmol). The resulting solution was then stirred at the same temperature. After 10 min, benzyl chloroformate (1.0 mL, 7.09 mmol) was added dropwise and the mixture was allowed to warm to room temperature. After 11 h, the reaction was quenched with saturated aq. $NaHCO_3$ solution and extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 4/1) to give **5a** (3.39 g, 84% yield) as pale yellow solid. Mp. 54−55 °C; IR (ATR) ν 3412, 1717, 1497, 1445, 1328, 1221, 1090, 1049, 850, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.34 (3H, s), 2.57−2.60 (1H, m), 3.11 (1H, broad peak), 3.37 (1H, d, J = 14.4 Hz), 3.55 (3H, s), 3.66 (1H, d, J = 14.4 Hz), 4.58−4.59 (2H, m), 4.83−4.87 (1H, m), 5.06 (1H, d, J = 12.0 Hz), 5.10 (1H, d, J = 12.0 Hz), 5.62 (1H, s), 6.82 (1H, d, J = 7.8 Hz), 6.96 (1H, s), 7.07 (1H, dd, J = 7.2, 7.8 Hz), 7.16 (2H, d, J = 8.4 Hz), 7.31−7.37 (5H, m), 7.50 (1H, d, J = 8.4 Hz), 7.59 (2 H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 34.7, 45.6, 52.5, 64.4, 66.5, 74.7, 83.6, 101.2, 121.2, 127.3, 127.3 (2C), 127.9, 128.2, 128.3 (2C), 128.5 (2C), 129.5 (2C), 135.8, 136.3, 137.8, 140.8, 144.1, 154.1, 172.0, 210.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{29}IN_2NaO_6S^+$ 683.0683; found 683.0684.

Compound 5b. This compound was prepared using the previously reported procedure.[4a]

Compound 6a. A solution of **5a** (1.06 g, 1.60 mmol), $Pd(dba)_2$ (92.0 mg, 0.16 mmol), PPh_3 (100 mg, 0.38 mmol), K_2CO_3 (884 mg, 6.4 mmol) in DMSO (160 mL) was heated at 90 °C in argon atmosphere for 4 h. The reaction mixture was cooled down to room temperature and quenched with saturated aq. NH_4Cl solution. After filtration through Celite, the filtrate was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 3/2) to give **6a** (613 mg, 72% yield) as white solid. mp. 90−91 °C; IR (ATR) ν 1724, 1596, 1496, 1443, 1353, 1240, 1162, 1048, 777, 657 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.31 (3H, s), 2.75−2.87 (2H, m), 3.18 (1H, d, J = 16.2 Hz), 3.63−3.65 (1H, m), 3.72 (3H, s), 4.47−4.55 (2H, m), 4.77 (1H, broad peak), 4.89 (1H, broad peak), 5.01 (1H, d, J = 12.6 Hz), 5.39 (1H, dd, J = 1.8, 6.0 Hz), 6.74 (1H, s), 7.10−7.15 (4H, m), 7.25−7.28 (4H, m), 7.58 (1H, d, J = 8.4 Hz), 7.62 (2H, d, J = 7.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.5, 38.5, 40.9, 52.9, 55.2, 57.0, 66.5, 113.4, 114.0, 125.9 (2C), 127.1 (2C), 127.5, 127.7, 128.0, 128.4 (2C), 129.7 (2C), 130.2, 133.0, 133.8, 134.1, 136.2, 144.2, 145.0, 154.9, 174.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{28}N_2NaO_6S^+$ 555.1560; found 555.1563.

Compound 6b. This compound was prepared using the previously reported procedure.[4a]

Compound 7a. **6a** (1.11 g, 2.08 mmol) and DDQ (1.13 g, 4.97 mmol) were dissolved in benzene (40 mL), and the resulting solution was refluxed for 4 h. The reaction mixture was cooled down to room temperature and then concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 3/1 to 5/2) to give **7a** (959 mg, 87% yield) as white solid. mp. 86−87 °C; IR (ATR) ν 1717, 1491, 1435, 1368, 1228, 1176, 1043, 732, 699, 663 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (3H, s), 3.44 (1H, d, J = 14.8 Hz), 3.60 (1H, d, J = 14.8 Hz), 3.72 (3H, s), 4.90 (1H, d, J = 11.6 Hz), 5.01 (1H, d, J = 11.6 Hz), 5.11 (1H, s), 6.28 (1H, d, J = 11.2 Hz), 6.63 (1H, d, J = 11.6 Hz), 7.00 (1H, d, J = 6.4 Hz), 7.17−7.35 (8H, m), 7.54 (1H, s), 7.78 (2H, d, J = 8.4 Hz), 7.86 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 41.1, 52.9, 61.5, 66.7, 99.8, 112.4, 119.5, 123.4, 125.1 (2C), 125.4, 126.8 (2C), 127.4, 127.8, 128.0, 128.4 (2C), 129.5, 129.9 (2C), 130.4, 134.8, 134.9, 135.9, 145.2, 154.9, 173.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{26}N_2NaO_6S^+$ 553.1404; found 553.1417.

Compound 7b. This compound was prepared from **6b**[4a] (703 mg, 1.41 mmol) according to the experimental procedure from **6a** to **7a**, and was obtained in 91% yield (639 mg). White solid; mp. 83−84 °C; IR (ATR) ν 1714, 1486, 1439, 1367, 1234, 1177, 1073, 755, 670, 616 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31 (9H, s), 2.33 (3H, s), 3.40 (1H, d, J = 14.8 Hz), 3.59 (1H, d, J = 14.4 Hz), 3.73 (3H, s), 4.86 (1H, s), 6.25 (1H, d, J = 11.6 Hz), 6.61 (1H, d, J = 11.2 Hz), 7.02 (1H, d, J = 6.8 Hz), 7.24−7.28 (3H, m), 7.54 (1H, s), 7.80 (2H, d, J = 7.6 Hz), 7.87 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 28.0 (3C), 41.1, 52.7, 61.3, 79.9, 112.3, 119.7, 121.0, 123.0, 124.8, 125.0 (2C), 125.3, 126.8 (2C), 127.4, 129.9, 130.7, 134.7, 134.9, 145.2, 154.4, 173.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{28}N_2NaO_6S^+$ 519.1560; found 519.1554.

Compound 8a. To a stirred solution of **7a** (860 mg, 1.62 mmol) in THF-MeOH (16.0 mL-3.2 mL) at 0 °C was added $LiBH_4$ (352 mg, 16.1 mmol). The resulting mixture was stirred for 30 min at the same temperature, and the reaction was quenched with water and extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate. After concentration *in vacuo*, the obtained residue was directly utilized for the next reaction. To a stirred solution of the crude product in CH_2Cl_2 (16.0 mL) at 0 °C was added trichloroacetyl isocyanate (0.23 mL, 1.94 mmol). After being stirred for 30 min at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (16.0 mL) and potassium carbonate (44 mg, 0.318 mmol) was added to the solution. After being stirred for 12 h at room temperature, the reaction was quenched with water and extracted with CH_2Cl_2. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 2/3) to give **8a** (830 mg, 94% yield) as white solid. Mp. 79−80 °C; IR (ATR) ν 1716, 1507, 1365, 1240, 1177, 1145, 1066, 742, 664, 615 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.32 (3H, s), 3.13 (1H, d, J = 14.8 Hz), 3.82 (1H, d, J = 14.8 Hz), 4.06 (1H, d, J

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= 11.6 Hz), 4.22 (1H, d, J = 11.6 Hz), 4.75−4.81 (2H, m), 4.96 (1H, d, J = 12.0 Hz), 5.04 (1H, d, J = 12.0 Hz), 5.52 (1H, s), 5.97 (1H, d, J = 12.0 Hz), 6.55 (1H, d, J = 12.0 Hz), 6.98 (1H, d, J = 6.8 Hz), 7.20−7.33 (8H, m), 7.51 (1H, s), 7.77 (2H, d, J = 8.4 Hz), 7.83 (1H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.4, 40.7, 52.1, 58.7, 66.5, 67.7, 99.9, 112.0, 119.8, 122.0, 124.8, 125.4, 126.8 (2C), 127.3, 127.9 (2C), 128.0, 128.4 (2C), 129.9 (2C), 130.6, 133.0, 135.1, 135.4, 136.5, 145.1, 156.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{27}N_3NaO_6S^+$ 568.1513; found 568.1504.

Compound 8b. This compound was prepared form **7b** (1.55 g, 3.12 mmol) according to the experimental procedure from **7a** to **8a**, and was obtained in 94% yield (1.51 g). White solid; mp. 95−96 °C; IR (ATR) ν 1714, 1596, 1366, 1246, 1176, 1064, 747, 664, 623, 613 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 1.35 (9H, s), 2.34 (3H, s), 3.12 (1H, d, J = 15.0 Hz), 3.83 (1H, broad peak), 4.04 (1H, d, J = 10.8 Hz), 4.19 (1H, d, J = 10.8 Hz), 4.71 (2H, broad peak), 5.18 (1H, s), 5.98 (1H, d, J = 12.0 Hz), 6.54 (1H, d, J = 11.4 Hz), 7.01 (1H, d, J = 7.2 Hz), 7.23−7.25 (3H, m), 7.50 (1H, s), 7.77 (2H, d, J = 7.8 Hz), 7.83 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6, 28.2 (3C), 40.7, 58.4, 67.7, 79.5, 111.8, 119.9, 121.5, 124.6, 124.8, 125.3, 126.8 (2C), 127.2, 129.9 (2C), 130.9, 133.6, 134.9, 135.1, 145.1, 154.5, 156.6; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{29}N_3NaO_6S^+$ 534.1669; found 534.1671.

Compound 9a. A solution of **8a** (153 mg, 0.281 mmol), $Rh_2(esp)_2$ (2.1 mg, 0.00276 mmol), $PhI(OAc)_2$ (162 mg, 0.502 mmol), MgO (25.9 mg, 0.642 mmol) in CH_2Cl_2 (5.6 mL) in argon atmosphere was warmed to 40 °C. After being stirred for 20 h at the same temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 2/3 to 1/2) to give **9a** (111 mg, 66% yield) as yellow solid. mp. 80−81 °C; IR (ATR) ν 1714, 1430, 1368, 1223, 1163, 1089, 1040, 813, 759, 662 cm^{-1}; ^{1}H NMR ($CDCl_3$, 600 MHz) δ 2.16 (3H, s), 2.31 (3H, s), 2.94 (1H, d, J = 15.0 Hz), 3.56 (1H, broad peak), 3.93−3.97 (2H, m), 4.54 (1H, d, J = 9.0 Hz), 4.93 (1H, d, J = 12.0 Hz), 5.02 (1H, d, J = 12.0 Hz), 5.47 (1H, s), 6.15 (1H, d, J = 7.8 Hz), 6.85−6.90 (2H, m), 7.17−7.31 (8H, m), 7.44 (1H, s), 7.76−7.80 (3H, m); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 20.7, 21.4, 34.4, 55.5, 61.8, 66.4, 67.2, 68.3, 112.6, 118.7, 122.9, 124.0, 125.6 (2C), 126.8, 127.5 (2C), 127.7, 128.0, 128.3, 128.3 (2C), 129.9 (2C), 134.4, 134.7, 135.8, 145.2, 154.0, 154.6, 170.2; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{31}H_{29}N_3NaO_8S^+$ 626.1568; found 626.1578. Note: When the reaction was performed using 509 mg of **8a**, **9a** was obtained in 61% yield (340 mg).

Compound 9b. This compound was prepared form **8b** (200 mg, 0.391 mmol) according to the experimental procedure from **8a** to **9a**, and was obtained in 67% yield (150 mg). White solid; mp. 130−131 °C; IR (ATR) ν 1714, 1523, 1369, 1223, 1176, 1089, 763, 681, 670, 621 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (9H, s), 2.25 (3H, s), 2.35 (3H, s), 2.96 (1H, d, J = 15.2 Hz), 3.52 (1H, broad peak), 3.98 (1H, broad peak), 4.05 (1H, d, J = 11.2 Hz), 4.63 (1H, d, J = 11.2 Hz), 4.78 (1H, s), 6.20 (1H, d, J = 8.4 Hz), 6.98 (1H, d, J = 7.2 Hz), 6.98 (1H, broad peak), 7.21−7.27 (3H, m), 7.42 (1H, s), 7.78−7.82 (3H, m); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 20.8, 21.5, 28.1 (3C), 34.3, 55.3, 62.3, 67.4, 68.4, 80.2, 112.5, 119.1, 122.4, 124.0, 125.6, 126.9 (2C), 127.6, 128.6, 130.0 (2C), 134.5, 134.8, 145.2, 154.0, 154.1, 170.3; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{28}H_{31}N_3NaO_8S^+$ 592.1724; found 592.1711. Note: When the reaction was performed using 589 mg of **8b**, **9b** was obtained in 62% yield (408 mg).

Compound 10a. To a stirred solution of **9a** (30.0 mg, 0.0496 mmol) in MeOH (1.0 mL) was added K_2CO_3 (6.8 mg). After being stirred for 1 h at room temperature, the reaction was quenched with water and extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate. After concentration *in vacuo*, the obtained residue was directly utilized for the next reaction. The residue was dissolved in chlorobenzene (1.0 mL), cooled to 0 °C, and then DPPA (53.4 μL, 0.247 mmol) and DBU (44.5 μL, 0.297 mmol) were added. The ice bath was removed and the reaction mixture was warmed to 60 °C, and then stirred for 14 h. The reaction mixture was cooled down to room temperature and diluted with AcOEt and water. The aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1) to give **10a** (10.7 mg, 36% yield) as white solid. mp. 114−115 °C; IR (ATR) ν 1704, 1364, 1253, 1176, 1142, 1070, 933, 702, 664, 620 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.35 (3H, s), 3.16 (1H, d, J = 15.2 Hz), 3.71 (1H, s), 3.87 (1H, d, J = 14.8 Hz), 4.15 (1H, d, J = 11.6 Hz), 4.46 (1H, d, J = 12.0 Hz), 4.95−5.04 (m, 3H), 5.30 (1H, s), 6.04 (1H, s), 6.91 (1H, d, J = 7.6 Hz), 7.20−7.33 (8H, m), 7.56 (1H, s), 7.78 (2H, d, J = 8.4 Hz), 7.82 (1H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 35.3, 57.4, 60.5, 61.4, 66.8, 69.2, 112.8, 116.6, 124.4, 124.8, 126.0, 126.9 (2C), 127.6, 128.0 (2C), 128.3, 128.6 (2C), 128.8, 130.1 (2C), 134.7, 134.9, 135.8, 145.5, 154.8, 155.0; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{26}N_6NaO_6S^+$ 609.1527; found 609.1539.

Compound 10b. This compound was prepared form **9b** (256 mg, 0.449 mmol) according to the experimental procedure from **9a** to **10a**, and was obtained in 63% yield (157 mg). White solid; mp. 120−121 °C; IR (ATR) ν 2110, 1716, 1486, 1366, 1250, 1177, 930, 878, 668, 610 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.35 (9H, s), 2.36 (3H, s), 3.17 (1H, d, J = 15.2 Hz), 3.73 (1H, s), 3.92 (1H, d, J = 15.2 Hz), 4.14 (1H, d, J = 11.2 Hz), 4.46 (1H, d, J = 11.2 Hz), 4.75 (1H, s), 5.17 (1H, s), 6.54 (1H, s), 6.97 (1H, d, J = 7.6 Hz), 7.23−7.27 (3H, m), 7.60 (1H, s), 7.80 (2H, d, J = 8.8 Hz), 7.84 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6, 28.1 (3C), 35.5, 57.2, 60.6, 61.7, 69.6, 80.5, 112.7, 116.9, 124.3, 124.7, 126.0, 126.9 (2C), 127.7, 129.2, 130.1 (2C), 134.7, 134.9, 145.5, 154.4, 155.4; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{28}N_6NaO_6S^+$ 575.1683; found 575.1683.

Compound 11. This compound was prepared form **9b** (20.5 mg, 0.0359 mmol) according to the experimental procedure from **9a** to **12**, and was obtained in 17% yield (3.7 mg). White solid; mp. 107−108 °C; IR (ATR) ν 3386, 1697, 1508, 1366, 1293, 1249, 1166, 1091, 755, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (9H, s), 1.44 (9H, s), 2.36 (3H, s), 3.00 (1H, d, J = 16.0 Hz), 3.21 (1H, broad peak), 3.62−3.77 (3H, m), 3.93 (1H, d, J = 9.6 Hz), 4.19−4.23 (1H, m), 5.11 (1H, d, J = 6.8 Hz), 5.26 (1H, d, J = 8.8 Hz), 5.81 (1H, s), 6.99 (1H, d, J = 7.2 Hz), 7.20−7.26 (3H, m), 7.71 (1H, s), 7.80 (2H, d, J = 8.4 Hz), 7.84 (1H, d, J = 8.8 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.6, 28.2 (3C), 28.2 (3C), 29.7, 38.7, 61.7, 65.1, 68.9, 80.0, 80.6, 111.8, 122.7, 124.5, 125.1, 125.4, 127.0 (2C), 127.1, 129.6, 130.0 (2C), 134.8, 135.0, 145.2, 155.7, 155.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{30}H_{39}N_3NaO_8S^+$ 624.2350; found 624.2352.

Compound 12. To a stirred solution of **9a** (140 mg, 0.231 mmol) and triethylamine (38 μL, 0.273 mmol) in CH_2Cl_2 (4.6 mL) at 0 °C was added DMAP (2.8 mg, 0.0229 mmol) and Boc_2O (150 mg, 0.687 mmol). After being stirred for 90 min at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in MeOH (7.6 mL), and 2 N aq. LiOH solution (1.4 mL) was added to the reaction mixture at 0 °C. After being stirred for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/2) to give **12** (78.8 mg, 65% yield) as white solid. mp. 112−113 °C; IR (ATR) ν 2923, 1738, 1369, 1241, 1175, 1087, 1043, 814, 762, 673 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.33 (9H, s), 2.33 (3H, s), 3.17 (1H, d, J = 16.0 Hz), 3.63 (1H, d, J = 16.0 Hz), 3.95 (1H, d, J = 9.2 Hz), 4.08 (1H, s), 4.16 (1H, d, J = 9.2 Hz), 4.46−4.53 (2H, m), 5.00 (1H, s), 6.42 (1H, s), 7.02 (1H, d, J = 6.8 Hz), 7.23−7.25 (3H, m), 7.67 (1H, s), 7.79 (2H, d, J = 8.4 Hz), 7.83 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 21.5, 28.1 (3C), 42.5, 60.0, 63.4, 67.8, 72.6, 80.8, 112.3, 120.2, 124.4, 125.5, 126.4, 126.9 (2C), 127.3, 128.6, 130.0 (2C), 134.7, 134.8, 145.4, 155.9, 158.7; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{29}N_3NaO_7S^+$ 550.1618; found 550.1625.

Compound 13. To a stirred solution of **12** (77.7 mg, 0.147 mmol) in toluene-DMF (3.0 mL-0.30 mL) at 0 °C was added DPPA (158 μL, 0.733 mmol) and DBU (121 μL, 0.809 mmol). The resulting mixture was stirred for 1 h at the same temperature, and the reaction was quenched with water and extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 2/1 to 1/1) to give **13** (68.1 mg, 84% yield) as white solid. Mp. 120−121 °C; IR (ATR) ν 2105, 1790, 1715, 1489,

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1367, 1249, 1176, 1088, 780, 664 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.43 (9H, s), 2.36 (3H, s), 3.14 (1H, d, J = 16.0 Hz), 3.57 (1H, d, J = 16.0 Hz), 4.11 (1H, d, J = 9.6 Hz), 4.37 (1H, dd, J = 3.2, 9.6 Hz), 4.63 (1H, d, J = 9.6 Hz), 4.95−5.00 (2H, m), 5.06 (1H, s), 7.06 (1H, d, J = 8.0 Hz), 7.25−7.32 (3H, m), 7.70 (1H, s), 7.81 (2H, d, J = 8.0 Hz), 7.91 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 21.6, 28.2 (3C), 42.8, 58.4, 59.9, 63.7, 73.9, 81.2, 112.8, 115.5, 125.0, 125.9, 126.0, 126.3, 127.1 (2C), 128.0, 130.2 (2C), 134.6, 135.2, 145.7, 155.7, 157.9; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{26}H_{28}N_6NaO_6S^+$ 575.1683; found 575.1669.

Compound 15. To a stirred solution of **13** (97.1 mg, 0.175 mmol) and in EtOH-H_2O (4.2 mL-1.4 mL) was added Zn powder (33.0 mg, 0.504 mmol) and NH_4Cl (27.0 mg, 0.504 mmol). After being stirred for 4 h at room temperature, the reaction mixture was diluted with AcOEt, and quenched with aq. NH_3 solution. The organic layer was separated and the aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate. After concentration *in vacuo*, the obtained residue was directly utilized for the next reaction. The residue was then dissolved in THF (3.4 mL), cooled to 0 °C, and 6-bromoindol-3-yl-oxo-acetyl chloride **14** (97.4 mg, 0.339 mmol) and triethylamine (35 μL, 0.252 mmol) were added successively. The ice bath was removed and the reaction mixture was stirred for 1 h at room temperature, then diluted with AcOEt and poured into water. The aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (*n*-hexane/AcOEt = 1/1 to 1/3) to give **15** (118.7 mg, 87% yield) as white solid. mp. 176−177 °C (decomp.); IR (ATR) ν 3336, 1765, 1637, 1507, 1363, 1240, 1177, 1024, 995, 664 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.23 (9H, s), 2.30 (3H, s), 3.15 (1H, d, J = 16.8 Hz), 3.39 (1H, d, J = 16.8 Hz), 3.97 (1H, d, J = 8.4 Hz), 4.17 (1H, d, J = 8.4 Hz), 4.30−4.34 (1H, m), 5.56−5.59 (1H, m), 6.95 (1H, d, J = 9.2 Hz), 7.05 (1H, d, J = 7.2 Hz), 7.26 (1H, dd, J = 7.2, 8.4 Hz), 7.37−7.42 (3H, m), 7.61 (1H, s), 7.75−7.77 (2H, m), 7.90 (2H, d, J = 6.8 Hz), 8.16 (1H, d, J = 8.4 Hz), 8.49 (1H, s), 8.74 (1H, s), 8.85 (1H, d, J = 8.4 Hz), 12.40 (1H, s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 21.3, 28.2 (3C), 41.0, 47.0, 58.6, 61.6, 75.8, 79.1, 111.3, 112.4, 115.7, 116.4, 119.2, 123.2, 124.6, 124.7, 124.9, 125.4, 125.9, 127.1, 127.4 (2C), 130.5 (2C), 130.9, 134.5, 134.9, 137.6, 139.7, 145.9, 157.1, 158.3, 163.6, 182.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{36}H_{34}BrN_5NaO_8S^+$ 798.1204; found 798.1208.

Compound 14. This compound was prepared using the reported procedure.[13]

Compound 16. To a stirred solution of **15** (30.0 mg, 0.0387 mmol) in MeOH-THF (0.40 mL-0.80 mL) was added Cs_2CO_3 (37.0 mg, 0.113 mmol). After being stirred for 22 h at room temperature, the reaction mixture was diluted with AcOEt and water. The aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 30/1 to 20/1) to give **16** (10.9 mg, 45% yield) as white solid and compound **15** was recovered (15.9 mg, 53% yield). mp. 179−180 °C; IR (ATR) ν 3300, 1747, 1634, 1496, 1438, 1413, 1242, 1159, 1050, 750 cm^{-1}; ^1H NMR (DMSO-d_6, 400 MHz) δ 1.33 (9H, s), 3.19 (1H, d, J = 16.4 Hz), 3.55 (1H, d, J = 16.4 Hz), 4.10 (1H, d, J = 8.4 Hz), 4.32−4.38 (2H, m), 5.70−5.73 (1H, m), 6.70 (1H, d, J = 8.8 Hz), 6.88 (1H, d, J = 7.2 Hz), 7.11 (1H, dd, J = 7.6, 8.0 Hz), 7.29−7.34 (2H, m), 7.48 (1H, dd, J = 1.6, 8.4 Hz), 7.81 (1H, s), 8.22 (1H, d, J = 8.4 Hz), 8.46 (1H, s), 8.55 (1H, d, J = 8.8 Hz), 8.93 (1H, d, J = 2.4 Hz), 11.26 (1H, d, J = 2.4 Hz), 12.45 (1H, s); ^{13}C NMR (DMSO-d_6, 150 MHz) δ 27.9 (3C), 41.0, 47.0, 58.8, 61.5, 76.1, 78.5, 109.6, 111.0, 112.0, 115.3, 115.9, 119.7, 121.2, 122.8, 123.6, 123.8, 125.2, 125.4, 128.4, 136.8, 137.2, 139.6, 156.6, 157.9, 162.5, 181.5; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{29}H_{28}BrN_5NaO_6^+$ 644.1115; found 644.1129.

Compound 18. To a stirred solution of **16** (9.6 mg, 0.0154 mmol) in CH_2Cl_2 (0.40 mL) at 0 °C was added TFA (0.10 mL). After being stirred for 1 h at room temperature, the reaction mixture was concentrated *in vacuo*. The obtained residue was dissolved in MeOH (4.0 mL) and warmed to 60 °C. After being stirred for 12 h at the same temperature, the reaction mixture was diluted with saturated aq. $NaHCO_3$ solution and AcOEt. The aqueous layer was extracted with AcOEt. The organic extracts were washed with brine, dried over sodium sulfate. After concentration *in vacuo*, the obtained residue was directly utilized for the next reaction. To a stirred solution of the crude product in dioxane (0.28 mL) was added DDQ (9.4 mg, 0.0414 mmol). After being stirred for 1 h at room temperature, the reaction was quenched with saturated aq. $NaHCO_3$ solution and extracted with AcOEt. The organic layer was washed with saturated aq. $NaHCO_3$ solution and brine, dried over sodium sulfate. After concentration *in vacuo*, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 20/1 to 10/1) to give **18** (6.9 mg, 89% yield) as bright yellow solid. mp. 192−193 °C (decomp.); IR (ATR) ν 3734, 1742, 1629, 1528, 1433, 1229, 1161, 883, 757, 638 cm^{-1}; ^1H NMR (DMSO-d_6, 600 MHz) δ 3.45 (1H, d, J = 15.0 Hz), 3.65 (1H, d, J = 15.0 Hz), 4.01 (1H, s), 4.15 (1H, broad peak), 7.03 (1H, d, J = 7.2 Hz), 7.16−7.20 (2H, m), 7.38 (1H, d, J = 8.4 Hz), 7.63 (1H, s), 8.22 (1H, s), 8.28 (1H, s), 8.72−8.75 (2H, m), 11.49 (1H, s), 11.81 (1H, s), 12.05 (1H, br-s); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 44.9, 62.7, 74.0, 110.8, 112.3, 114.0, 114.1, 114.7, 114.8, 121.4, 122.1, 122.3, 122.7, 123.0, 123.9, 124.7, 125.2, 126.4, 128.0, 131.0, 136.0, 137.1, 154.9, 158.1; HRMS (ESI-TOF) m/z: $[M+Na]^+$ Calcd for $C_{24}H_{16}BrN_5NaO_3^+$ 524.0329; found 524.0341.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00083.

^1H and ^{13}C NMR charts of new compounds (PDF)

X-ray crystallographic data for compound **10b** (CIF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) Capon, R. J.; Rooney, F.; Murray, L. M.; Collins, E.; Sim, A. T. R.; Rostas, J. A. P.; Butler, M. S.; Carroll, A. R. *J. Nat. Prod.* **1998**, *61*, 660.

(2) (a) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2005**, *7*, 5449. (b) Huntley, R. J.; Funk, R. L. *Org. Lett.* **2006**, *8*, 4775. (c) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2010**, *12*, 4502. (d) Wang, B.; Qin, H.; Zhang, F.; Jia, Y. *Tetrahedron Lett.* **2014**, *55*, 1561.

(3) Feldman, K. S.; Ngernmeesri, P. *Org. Lett.* **2011**, *13*, 5704.

(4) (a) Nakano, S.; Inoue, N.; Hamada, Y.; Nemoto, T. *Org. Lett.* **2015**, *17*, 2622. (b) Suzuki, Y.; Tanaka, Y.; Nakano, S.; Dodo, K.; Yoda, N.; Shinohara, K.; Kita, K.; Kaneda, A.; Sodeoka, M.; Hamada, Y.; Nemoto, T. *Chem. - Eur. J.* **2016**, *22*, 4418.

(5) Cazes, B.; Djahanbini, D.; Goré, J.; Genêt, J.-P.; Gaudin, J.-M. *Synthesis* **1988**, *1988*, 983.

(6) When the methyl ester in **7a** was treated with general reduction conditions (DIBAL-H, CH_2Cl_2, − 78 °C), the primary alkoxide generated in the reaction mixture sequentially reacted with the carbonyl group in Cbz unit, providing the corresponding cyclic carbamate as a major product.

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(7) For representative examples, see: (a) Guthikonda, K.; Du Bois, J. *J. Am. Chem. Soc.* **2002**, *124*, 13672. (b) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (c) Wehn, P. M.; Du Bois, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 3802. (d) Boralsky, L. A.; Marston, D.; Grigg, R. D.; Hershberger, J. C.; Schomaker, J. M. *Org. Lett.* **2011**, *13*, 1924. (e) Unsworth, W. P.; Clark, N.; Ronson, T. O.; Stevens, K.; Thompson, A. L.; Lamont, S. G.; Robertson, J. *Chem. Commun.* **2014**, *50*, 11393. (f) Jat, J. L.; Paudyal, M. P.; Gao, H.; Xu, Q.-L.; Yousufuddin, M.; Devarajan, D.; Ess, D.; Kürti, L.; Falck, J. R. *Science* **2014**, *343*, 61.

(8) For a review on nucleophilic ring opening of aziridines, see: Hu, X. E. *Tetrahedron* **2004**, *60*, 2701.

(9) For related rhodium-catalyzed cascade processes, see: (a) Padwa, A.; Stengel, T. *Org. Lett.* **2002**, *4*, 2137. (b) Sato, S.; Shibuya, M.; Kanoh, N.; Iwabuchi, Y. *Chem. Commun.* **2009**, 6264. (c) Guasch, J.; Díaz, Y.; Matheu, I.; Castillón, S. *Chem. Commun.* **2014**, *50*, 7344.

(10) For examples of transition metal-catalyzed aminoacetoxylation of olefins. Pd catalysis: (a) Alexanian, E. J.; Lee, C.; Sorensen, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 7690. (b) Liu, G.; Stahl, S. S. *J. Am. Chem. Soc.* **2006**, *128*, 7179. (c) Li, J.; Grubbs, R. H.; Stoltz, B. M. *Org. Lett.* **2016**, *18*, 5449. Cu catalysis: (d) Mancheno, D. E.; Thornton, A. R.; Stoll, A. H.; Kong, A.; Blakey, S. B. *Org. Lett.* **2010**, *12*, 4110. (e) Sanjaya, S.; Chiba, S. *Org. Lett.* **2012**, *14*, 5342.

(11) (a) Thompson, A. S.; Humphrey, G. R.; DeMarco, A. M.; Mathre, D. J.; Grabowski, E. J. J. *J. Org. Chem.* **1993**, *58*, 5886. (b) Mizuno, M.; Shioiri, T. *Chem. Commun.* **1997**, 2165.

(12) Compound **10b** was recrystallized from a *n*-hexane-ethyl acetate mixed solvent and compound **10b** formed a cocrystal with a single molecule of ethyl acetate. Crystal data of **10b**·AcOEt (CCDC 1525672): Colorless block crystal; $C_{26}H_{28}N_6O_6S$, $C_4H_8O_2$; M = 640.71; monoclinic; a = 16.9808(5), b = 19.2205(5), c = 9.7931(3) Å, V = 3153.57(15) Å^3; T = − 180 °C; space group $P2_1/c$ (#14); Z = 4, 32833 reflections measured, 5749 unique (R_{int} = 0.1178); R1 = 0.0714; wR2 = 0.1556.

(13) Guinchard, X.; Vallée, Y.; Denis, J.-N. *Org. Lett.* **2007**, *9*, 3761.

(14) (a) Hinman, A.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 11510. (b) Fuse, S.; Koinuma, H.; Kimbara, A.; Izumikawa, M.; Mifune, Y.; He, H.; Shin-ya, K.; Takahashi, T.; Doi, T. *J. Am. Chem. Soc.* **2014**, *136*, 12011. (c) Wang, B.; Liu, Y.; Jiao, R.; Feng, Y.; Li, Q.; Chen, C.; Liu, L.; He, G.; Chen, G. *J. Am. Chem. Soc.* **2016**, *138*, 3926.

DOI: 10.1021/acs.joc.7b00083
J. Org. Chem. 2017, 82, 2787−2793