Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 9447–9454

TETRAHEDRON

Synthetic study on indolic enamides

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Received 17 July 2003; accepted 5 September 2003

Abstract—We report a facile method for preparing enamides, based on the Curtius rearrangement and acylation of alkenylcarbamate. Using this approach, total syntheses of coscinamides, chondriamides, and igzamide were achieved.

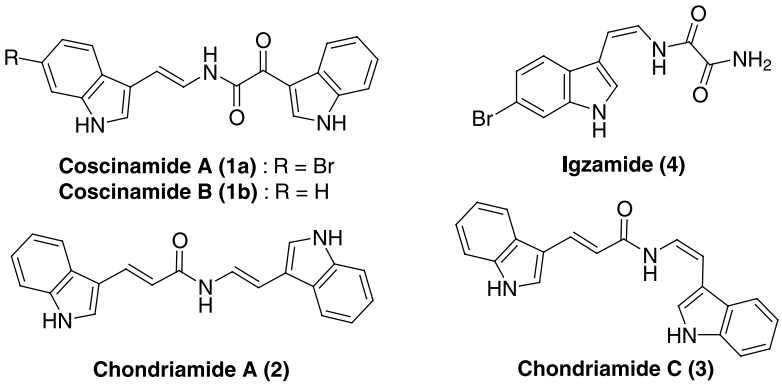
1. Introduction

Many indolic natural products which have an enamide moiety in the side chain have been isolated recently (Scheme 1). These compounds have been known to show attractive activities. For example, coscinamide A (**1a**) and B (**1b**) are bis-indole-containing marine natural products that show HIV-inhibitory activity.[1] Chondriamide A (**2**) shows cytotoxity against KB and LOVO cells and antiviral activity against HSV II.[2] Chondriamide C (**3**) shows both cytotoxity and anthelmintic activity.[2] Igzamide (**4**) shows cytotoxicity against the murine leukemia L1210.[3]

Even though various methods for constructing the enamide moiety have been reported,[4] including acylation of imines,[5] condensation of amides and aldehydes,[6] Beckmann rearrangement,[7] isomerization of *N*-allylamides[8] and addition of amides to alkenes or alkynes,[9] to the best of our knowledge, little is known of the stereoselective synthesis of (*Z*)-enamides,[10] particularly, indolic enamide compounds.

We have previously reported the stereoselective synthesis of enamide using Curtius rearrangement and organometallic addition to the isocyanate.[11] Its utility was shown by the construction of the side chain moieties of salicylihalamides, oximidines, lobatamides, CJ-12950 and CJ-13357.[11,12] This methodology was also proved to be efficient through the recent total syntheses of enamide natural products.[12b,13]

However, our initial approach incurred difficulties in the synthesis of these natural products. In fact, during the course of our synthetic study on coscinamides and chondriamides, our initial approach proved unsuccessful.[14] The synthesis of indolic enamide natural products by this methodology was difficult. So, we needed to establish methodology suitable for these targeted compounds. Herein, we report total syntheses of coscinamides, chondriamides and igzamide using a newly developed approach.



Scheme 1.

Keywords: indolic enamides; Curtius rearrangement; acylation.
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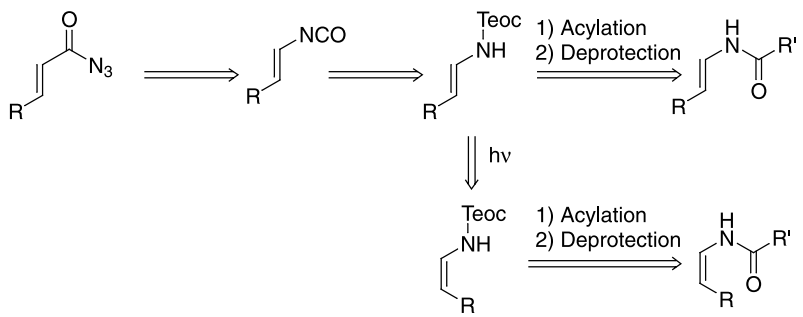
doi:10.1016/j.tet.2003.09.011



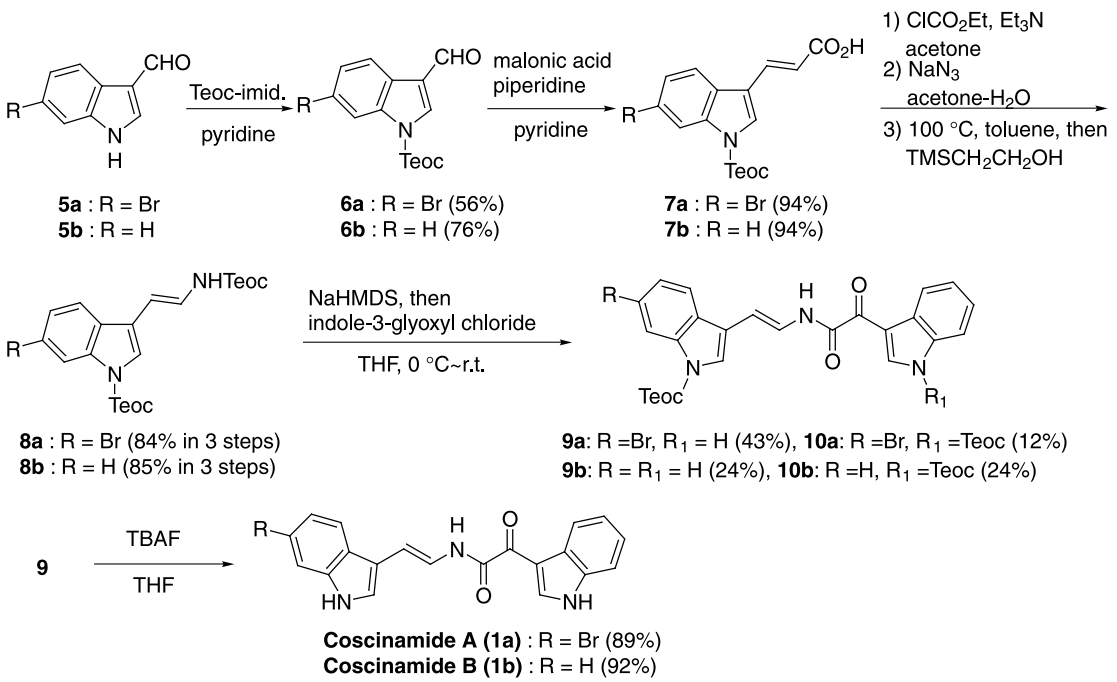
Scheme 2.

Our new plan to construct enamides is outlined in Scheme 2. (*E*)-Alkenyl isocyanate could be trapped with 2-(trimethylsilyl)ethanol to form (*E*)-*N*-[2-(trimethylsilyl)ethoxycarbonyl]-protected (Teoc-protected) enamine. (*Z*)-Enecarbamate could be obtained by photoisomerization of (*E*)-enecarbamate. Acylation of the carbamate and deprotection of the Teoc groups could give the desired enamide with retention of the configuration. Smith III and his co-worker have recently reported a total synthesis of (+)-salicylihalamide using this approach.[15] And Rizzacasa accomplished the synthesis of (+)-crocacin D, which contains the (*Z*)-enamide moiety using a similar approach.[16] The most significant feature of this approach is that (*E*)- and (*Z*)-*N*-Teoc-protected enamines serve as potential intermediates for the synthesis of various indolic enamide products.

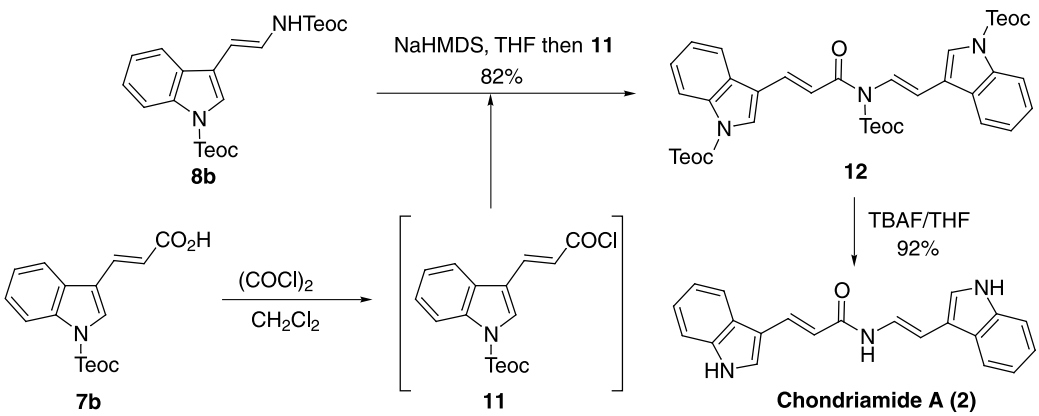
2. Result and discussion

Indole-3-carbaldehyde (**5b**) was first protected as the Teoc-carbamate by using Roush's method[17] to give **6b** in 76% yield (Scheme 3). Condensation of **6b** with malonic acid in the presence of piperidine provided (*E*)-*N*-Teoc-3-indoleacrylic acid (**7b**).[18] Treatment of **7b** with $ClCO_2Et$ and Et_3N in acetone, followed by addition of NaN_3 gave the acyl azide.[19] After thermal decomposition of the acyl azide, the intermediate isocyanate was trapped with 2-(trimethylsilyl)ethanol to give **8b** in 85% yield in three steps. With *N*-Teoc-alkenylcarbamate (**8b**) in hand, we moved to the acylation step. Treatment of **8b** with NaHMDS in THF, followed by addition of commercially available 3-indoleglyoxyl chloride gave **9b** in 24% yield and **10b** in 24% yield. And 32% of **8b** was recovered. Although the use of other bases (NaH, *n*-BuLi, LiHMDS, *t*-BuOK, KHMDS, $CsCO_3$ in the presence of 18-crown-6, DBU, Et_3N, DMAP in pyridine) was investigated, none or only a trace amount of **9b** was obtained. Using methyl 3-indoleglyoxalate instead of 3-indoleglyoxyl chloride was unsuccessful.[20] Deprotecton of the Teoc group was accomplished by treatment of **9b** with TBAF to afford coscinamide B (**1b**). In the same way, coscinamide A (**1a**) was synthesized from 6-bromoindole-3-carboaldehyde (**5a**) (Scheme 3).

Chondriamide A (**2**) was also synthesized from the key intermediate **8b** (Scheme 4). *N*-Teoc-3-indoleacryloyl chloride (**11**) was prepared by treatment of indol-3-yl acrylic acid (**7b**) with oxalyl chloride. Treatment of **8b** with



Scheme 3.

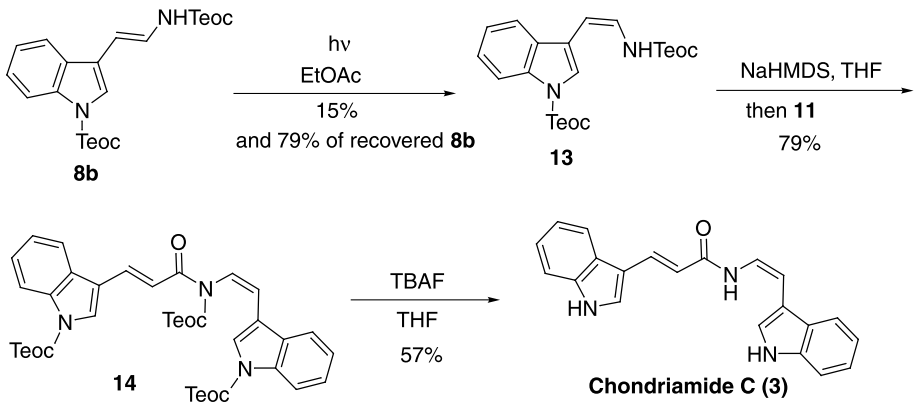


Scheme 4.

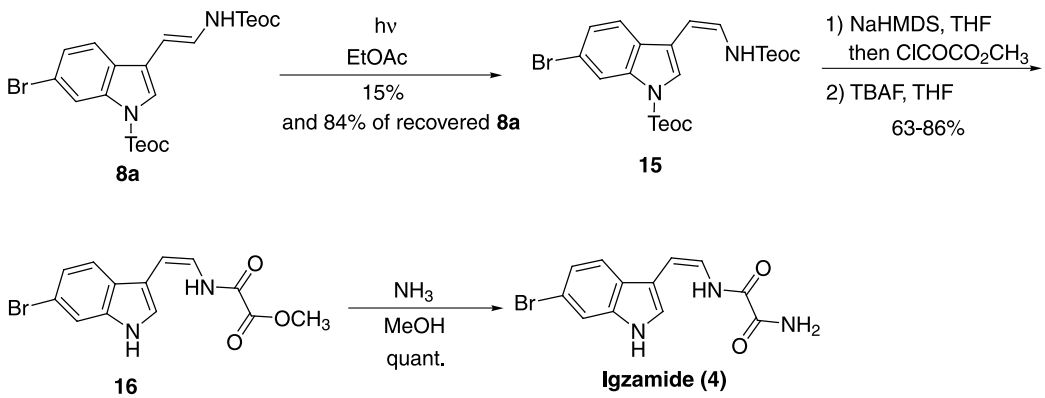
NaHMDS in THF, followed by addition of **11** in THF gave the desired enamide **12** in 82% yield. Exposure of **12** to TBAF in THF provided chondriamide A (**2**).

Next we attempted to synthesize chondriamide C (**3**) and igzamide (**4**), which contain (*Z*)-enamide. At first, we undertook the synthesis of condriamide C (**3**) (Scheme 5). Irradiation of **8b** with a high-pressure mercury arc lamp afforded a mixture of (*E*)- and (*Z*)-alkenylcarbamate, which were easily separated by silica gel chromatography. Treatment of (*Z*)-alkenylcarbamate (**13**) with NaHMDS, followed by addition of **11** gave **14** in 79% yield. And deprotecton of the Teoc group with TBAF afforded chondriamide C (**3**) in 57% yield. During the acylation of (*Z*)-enecarbamate and deprotection of the Teoc groups, retention of the (*Z*)-configuration was established by the coupling constants and a comparison of the ^{1}H and ^{13}C NMR spectra between the synthetic chondriamide C (**3**) and the natural product.

In the same way, igzamide was synthesized from enecarbamate (**8a**). Photoisomerization of **8a** gave (*Z*)-enecarbamate **15** in 15% yield (84% of **8a** was recovered). Treatment of **15** with NaHMDS in THF, followed by addition of methyl chlorooxoacetate gave the Teoc-protected enamine. Since this Teoc-protected enamine was unstable to silica gel, deprotection of the Teoc groups was conducted without further purification. Treatment of the Teoc-protected



Scheme 5.



Scheme 6.

enamine with TBAF afforded **16** after chromatographic purification. Finally, treatment of **16** with liq. NH_3 in MeOH gave igzamide (**4**).

3. Conclusion

In summary, we have shown the total synthesis of coscinamide A, B and chondriamide A, C and igzamide using a newly developed approach, which involved acylation of Teoc-protected enamines and deprotection of the Teoc group. The IR, ^1H and ^{13}C NMR spectral data were in good accordance with those of the natural product.[1–3] Enecarbamates **8a**, **8b**, **13** and **15** serve as potential intermediates for the synthesis of various indolic enamide products. Synthetic studies of other indolic enamides as well as analogs using this methodology are currently under way (Scheme 6).

4. Experimental

4.1. General

IR spectra were measured as films for oils or KBr disc for solids on a Jasco FT/IR-230 spectrometer. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded with solvent peak as an internal standard on a JEOL JNM-AL300 spectrometer unless otherwise stated. HRMS (FAB) were measured on a JEOL JMS-HX110 (ion acceleration voltage was 10 kV, and the fast-atom xenon gas was accelerated at a voltage of 3 kV). Column was carried out columns packed with Kanto Chemical Co. Inc. silica gel 60N 63–210 μm unless otherwise stated. Preparative TLC was carried out with Merk Kieselgel $60F_{254}$ 1.05744. THF was purified by distillation from benzophenone ketyl. CH_2Cl_2 was purified by distillation from P_2O_5.

4.1.1. *N*-[(2-Trimethylsilylethoxy)carbonyl]indole-3-carbaldehyde (6b). A mixture of indole-3-carbaldehyde **5b** (10 g, 70 mmol) and 2-(trimethylsilyl)ethoxycarbonylimidazole (22 g, 104 mmol) in pyridine (50 ml) was stirred at 50°C for 48 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel by eluting with 15% EtOAc in hexane to afford 15 g (53 mmol, 76%) of **6b** as a white solid. Mp 104°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.12 (9H, s), 1.25 (2H, m), 4.57 (2H, m), 7.35 (1H, dt, J=1.2, 7.5 Hz), 7.40 (1H, dt, J=1.5, 7.5 Hz), 8.17 (1H, dd, J=1.5, 7.5 Hz), 8.19 (1H, s), 8.27 (1H, dd, J=7.5 Hz. 1.2 Hz), 10.1 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.6, 17.8, 67.0, 115.1, 121.9, 122.0, 124.7, 126.1, 135.9, 136.0, 150.3, 185.6; IR (KBr): 3020, 2958, 1747, 1678, 1553, 1453, 1400, 1346, 1238, 1216, 1092, 840, 771 cm^{-1}; HRMS: calcd for $C_{15}H_{19}NO_3Si$ (M^+) 289.1134, found 289.1133.

4.1.2. *N*-[(2-Trimethylsilylethoxy)carbonyl]-6-bromoindole-3-carbaldehyde (6a). A mixture of 6-bromoindole-3-carbaldehyde **5a** (0.83 g, 3.7 mmol) and 2-(trimethylsilyl)ethoxycarbonylimidazole (1.7 g, 7.9 mmol) in pyridine (10 ml) was stirred at 50°C for 14 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel by eluting with 15% EtOAc in hexane to afford 0.76 g (2.1 mmol, 56%) of **6a** as a white solid and 0.37 g (1.5 mmol, 44%) of **5a** was recovered. Mp 79–80°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.12 (9H, s), 1.25 (2H, m), 4.58 (2H, m), 7.45 (1H, dd, J=1.8, 8.4 Hz), 8.09 (1H, d, J=8.4 Hz), 8.15 (1H, s), 8.31 (1H, d, J=1.8 Hz), 10.0 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.6, 17.7, 67.5, 118.2, 119.9, 121.5, 123.2, 124.7, 128.0, 136.4, 149.8, 185.2; IR (KBr): 3138, 2955, 2909, 1752, 1683, 1549, 1461, 1429, 1396, 1342, 1230, 1142, 1094, 930, 838, 761, 700 cm^{-1}; HRMS: calcd for $C_{15}H_{19}{}^{79}BrNO_3$ ($[M+H]^+$) 368.0318, found 368.0316.

4.1.3. (*E*)-3-{1-[(2-Trimethylsilylethoxy)carbonyl]-indole}acrylic acid (7b). A mixture of **6b** (0.63 g, 2.2 mmol) and malonic acid (0.72 g, 6.9 mmol) and a catalytic amount of piperidine in pyridine (4 ml) was stirred at 80°C for 3 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel by eluting with 20% EtOAc in hexane to afford 0.68 g (2.1 mmol, 94%) of acrylic acid **7b** as a white solid. Mp 169–170°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.13 (9H, s), 1.26 (2H, t, J=9.0 Hz), 4.56 (2H, t, J=9.0 Hz), 6.56 (1H, d, J=16.2 Hz), 7.34–7.44 (2H, m), 7.85–7.95 (3H, m), 8.25 (1H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, 17.7, 66.5, 115.6, 117.0, 120.3, 123.9, 125.5, 127.7, 128.9, 136.2, 138.7, 150.5, 172.7; IR (KBr): 3800–3200, 3119, 2955, 1739, 1678, 1624, 1549, 1452, 1391, 1254, 1215, 930, 840, 747 cm^{-1}; HRMS: calcd for $C_{17}H_{22}NO_4Si$ ($[M+H]^+$) 332.1318, found 332.1367.

4.1.4. (*E*)-3-{1-[(2-Trimethylsilylethoxy)carbonyl]-6-bromoindole}acrylic acid (7a). A mixture of **6a** (1.4 g, 3.7 mmol) and malonic acid (1.4 g, 13 mmol) and a catalytic amount of piperidine in pyridine (8 ml) was stirred at 80°C for 3 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was chromatographed on silica gel by eluting with 20% EtOAc in hexane to afford 1.4 g (3.5 mmol, 94%) of acrylic acid **7a** as a white solid. Mp 173°C; ^1H NMR ($CDCl_3$, 300 MHz): δ 0.13 (9H, s), 1.25 (2H, m), 4.56 (2H, m), 6.56 (1H, d, J=15.9 Hz), 7.48 (1H, dd, J=8.4, 1.5 Hz), 7.87 (1H, d, J=15.9 Hz), 7.88 (1H, s), 8.43 (1H, d, J=1.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, 17.7, 67.0, 116.8, 117.0, 118.8, 119.4, 121.3, 126.5, 127.2, 129.0, 136.8, 138.0, 150.2, 171.8; IR (KBr): 3677, 3020, 1742, 1739, 1688, 1632, 1546, 1431, 1391, 1354, 1216, 1096, 930, 840, 768, 699 cm^{-1}; HRMS: calcd for $C_{17}H_{20}{}^{79}BrNO_4Si$ ($[M+H]^+$) 409.0345, found 409.0316.

4.1.5. 2-Trimethylsilylethyl *N*-[(*E*)-2-{[(2-trimethylsilylethoxy)carbonyl]indol-1-yl}ethenyl]carbamate (8b). To a solution of **7b** (0.54 g, 1.6 mmol), Et_3N (0.21 ml, 2.2 mmol) in acetone (10 ml) was added $ClCO_2Et$ (0.30 ml, 2.2 mmol)

and the mixture was stirred at 0°C for 30 min. Then a solution of NaN_3 (0.13 g, 2.0 mmol) in H_2O (1.5 ml) was added to the mixture at 0°C. The mixture was stirred at 0°C for 20 min. Then the reaction was quenched by the addition of H_2O and the resulting mixture was diluted with $CHCl_3$. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. A solution of the residue in toluene (5 ml) was stirred at 100°C for 1 h and added 0.5 ml of 2-(trimethylsilyl)ethanol. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel by eluting with 14% EtOAc in hexane to afford 0.61 g (1.4 mmol, 85%) of carbamate **8b** as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.07 (9H, s), 0.11 (9H, s), 1.04 (2H, m), 1.23 (2H, m), 4.27 (2H, m), 4.51 (2H, m), 6.05 (1H, d, J=15.0 Hz), 6.51 (1H, dd, J=10.2 Hz), 7.24–7.35 (3H, m), 7.55 (1H, s), 7.70 (1H, d, J=7.5 Hz), 8.54 (1H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, −1.5, 17.7, 17.7, 64.0, 65.7, 101.3, 115.3, 117.7, 119.7, 121.2, 123.0, 124.6, 124.8, 128.7, 135.8, 151.0, 153.7; IR (neat): 3320, 2954, 2899, 1731, 1566, 1504, 1454, 1393, 1250, 1048, 944, 837, 760, 695 cm^{-1}; HRMS: calcd for $C_{22}H_{35}N_2O_4Si_2$ ([M+H]$^+$) 446.2057, found 446.2049.

4.1.6. 2-Trimethylsilylethyl *N*-[(*E*)-2-{[(2-trimethylsilylethoxy)carbonyl]-6bromoindol-1-yl}ethenyl]carbamate (8a). To a solution of **7a** (1.4 g, 3.3 mmol), Et_3N (0.63 ml, 4.5 mmol) in acetone (8 ml) was added $ClCO_2Et$ (0.44 ml, 2.2 mmol) and the mixture was stirred at 0°C for 40 min. Then a solution of NaN_3 (0.33 g, 5.1 mmol) in H_2O (2 ml) was added to the mixture at 0°C. The mixture was stirred at 0°C for 20 min. Then the reaction was quenched by the addition of H_2O and the resulting mixture was diluted with $CHCl_3$. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. A solution of the residue in toluene (8 ml) was stirred at 100°C for 1.8 h and added 2.0 ml of 2-(trimethylsilyl)-ethanol. The solvent was evaporated in vacuo and the residue was chromatographed on silica gel by eluting with 14% EtOAc in hexane to afford 1.5 g (2.8 mmol, 84%) of carbamate **8a** as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.07 (9H, s), 0.11 (9H, s), 1.04 (2H, m), 1.22 (2H, m), 4.26 (2H, m), 4.52 (2H, m), 5.99 (1H, d, J=14.7 Hz), 6.54 (1H, dd, J=11.4 Hz), 7.38 (1H, dd, J=1.8, 8.4 Hz), 7.50–7.54 (2H, m), 8.34 (1H, brs); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, −1.5, 17.7, 17.7, 64.1, 66.1, 100.7, 117.6, 118.5, 120.8, 121.4, 125.0, 126.2, 127.6, 136.4, 150.6, 153.7; IR (neat): 4213, 3432, 3329, 3020, 2956, 2900, 1728, 1666, 1602, 1556, 1434, 1394, 1249, 1218, 1064, 941, 860, 839, 763 cm^{-1}; HRMS: calcd for $C_{22}H_{34}{}^{81}BrO_4Si_2$ ([M+H]$^+$) 527.1220, found 527.1202.

4.1.7. *N*-Teoc coscinamide B (9b) and *N*,*N*′-bis-Teoc coscinamide B (10b). To a solution of carbamate **8b** (108 mg, 0.24 mmol) in THF (6 ml) was added a solution of NaHMDS (1 M solution in THF, 730 μl, 0.73 mmol) at 0°C for 10 min. Then 3-indoleglyoxyl chloride (100 mg, 0.48 mmol) was added to the mixture at 0°C. The mixture was stirred at room temperature for 1 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by PTLC (hexane/EtOAc=7:1) to yield 28 mg (0.059 mmol, 24%) of **9b**, 36 mg (0.058 mmol, 24%) of **10b**. And 34 mg (32%) of **8b** was recovered.

Compound **9b**. Yellow needle. Mp 162–164°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.10 (9H, s), 1.23 (2H, m), 4.51 (2H, m), 6.49 (1H, d, J=14.7 Hz), 7.27–7.54 (5H, m), 7.58 (1H, dd, J=14.7, 11.1 Hz), 7.65 (1H, s), 7.77 (1H, dd, J=6.6, 0.9 Hz), 8.21 (1H, d, J=8.4 Hz), 8.44 (1H, m), 8.91 (1H, brs), 9.12 (1H, d, J=3 Hz), 9.31 (1H, d, J=11.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, 17.8, 65.9, 107.6, 111.7, 113.3, 115.4, 117.4, 119.9, 121.6, 122.5, 122.7, 123.2, 123.6, 124.4, 125.0, 126.6, 128.4, 135.7, 138.4, 150.9, 179.4; IR (KBr): 4214, 3263, 3020, 2957, 2398, 1726, 1656, 1627, 1456, 1396, 1248, 1217, 942, 861, 839 cm^{-1}; HRMS: calcd for $C_{26}H_{27}N_3O_4Si$ ([M+H]$^+$) 474.1849, found 474.1884.

Compound **10b**. Yellow needle. Mp 159–161°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.10 (9H, s), 0.11 (9H, s), 1.20–1.30 (4H, m), 4.59–4.61 (4H, m), 6.52 (1H, d, J=15.0 Hz), 7.28–7.34 (2H, m), 7.37–7.46 (2H, m), 7.58 (1H, dd, J=15.0, 11.1 Hz), 7.65 (1H, s), 7.78 (1H, d, J=8.1 Hz), 8.20–8.27 (2H, m), 8.38–8.41 (1H, m), 9.17 (1H, d, J=11.1 Hz), 9.46 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, −1.5, 17.8, 17.8, 65.9, 67.2, 108.1, 115.2, 115.5, 115.6, 117.2, 120.0, 121.3, 122.4, 122.9, 123.3, 124.1, 125.0, 125.3, 126.1, 126.4, 127.8, 128.2, 135.2, 138.6, 150.2, 152.1, 157.9, 180.8; IR (neat): 3352, 2957, 1744, 1685, 1645, 1454, 1396, 1351, 1233, 1098, 1047, 941, 862, 837, 753 cm^{-1}; HRMS: calcd for $C_{32}H_{40}N_3O_6Si_2$ ([M+H]$^+$) 618.2456, found 618.2468.

4.1.8. Coscinamide B (1b). To a solution of **9b** (19.5 mg, 0.041 mmol) in THF (1.5 ml) was added a solution of TBAF (1 M solution in THF, 45 μl, 0.045 mmol) at 0°C. After the mixture was stirred at room temperature for 30 min, the reaction was quenched by adding H_2O. The resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by PTLC (hexane/EtOAc=1:1) to yield 12.5 mg (0.038 mmol, 92%) of coscinamide B (**1b**); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.85 (1H, d, J=14.7 Hz), 7.07–7.16 (2H, m), 7.27 (1H, m), 7.29 (1H, m), 7.39 (1H, d, J=7.2 Hz), 7.42 (1H, dd, J=14.7, 10.2 Hz), 7.48 (1H, s), 7.53–7.56 (1H, m), 7.69 (1H, d, J=6.9 Hz), 8.25–8.29 (1H, m), 8.83 (1H, s), 10.81 (1H, d, J=10.2 Hz), 11.19 (1H, s), 12.29 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 111.0, 111.6, 111.9, 112.3, 112.6, 118.6, 119.0, 119.4, 121.3, 121.6, 122.7, 123.5, 124.3, 124.8, 126.3, 136.3, 136.9, 138.6, 160.3, 181.1; IR (KBr): 4213, 3222, 3013, 2928, 2461, 2400, 2253, 2126, 1672, 1626, 1543, 1489, 1441, 1216, 1027, 940, 768 cm^{-1}; HRMS: calcd for $C_{20}H_{16}N_3O_2$ ([M+H]$^+$) 330.1240, found 330.1243.

4.1.9. *N*-Teoc coscinamide A (9a) and *N*,*N*′-bis-Teoc coscinamide A (10a). Carbamate **8a** (232 mg, 0.44 mmol) was converted to 104 mg (0.19 mmol, 43%) of *N*-Teoc coscinamide A (**9a**) and 37 mg (0.035 mmol, 12%) of *N*,*N*′-bis-Teoc coscinamide A (**10a**) and recovered 92 mg (40%) of recovered **8a** according to the procedure described for the conversion of carbamate **8b** to *N*-Teoc coscinamide B (**9b**) and *N*,*N*′-bis-Teoc coscinamide B (**10b**).

Compound **9a**. Yellow needle. Mp 173–175°C; ^{1}H NMR (acetone-d_6, 300 MHz): δ 0.12 (9H, s), 1.29 (2H, m), 4.56 (2H, m), 6.87 (1H, dd, J=15.0, 0.9 Hz), 7.25–7.32 (2H, m), 7.50 (1H, dd, J=2.1, 8.4 Hz), 7.58 (1H, m), 7.61 (1H, dd, J=7.2, 15.0 Hz), 7.75 (1H, d, J=8.4 Hz), 7.79 (1H, s), 8.36 (1H, m), 8.40 (1H, d, J=1.5 Hz), 9.07 (1H, d, J=3.3 Hz), 10.17 (1H, d, J=7.2 Hz), 11.44 (1H, brs); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, 18.1, 66.8, 106.9, 113.2, 113.6, 118.6, 118.8, 118.9, 122.1, 122.7, 123.6, 123.7, 123.9, 124.6, 127.0, 127.7, 128.4, 137.3, 137.5, 139.6, 151.1, 160.9, 180.6; IR (KBr): 4209, 3421, 3322, 3186, 3020, 2954, 2395, 1725, 1658, 1607, 1553, 1490, 1447, 1263, 1215, 1138, 936, 836, 757 cm^{-1}; HRMS: calcd for $C_{26}H_{26}BrN_3O_4Si$ (M^+) 551.0876, found 551.0916.

Compound **10a**. Yellow solid. Mp 181°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.13 (9H, s), 0.13 (9H, s), 1.21–1.31 (4H, m), 4.49–4.61 (4H, m), 4.49–4.61 (4H, m), 6.45 (1H, d, J=14.4 Hz), 7.38–7.48 (3H, m), 7.52 (1H, dd, J=11.1, 14.1 Hz), 7.53 (1H, s), 7.60 (1H, d, J=8.4 Hz), 8.24 (1H, dd, J=2.4, 6.6 Hz), 8.36–8.38 (2H, m), 9.19 (1H, d, J=11.1 Hz), 9.42 (1H, s); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5, −1.5, 17.8, 17.8, 66.3, 67.2, 107.4, 115.2, 115.5, 115.6, 117.0, 118.6, 118.8, 120.9, 121.6, 122.3, 123.1, 125.0, 125.3, 126.1, 126.4, 127.1, 127.7, 135.1, 138.6, 150.2, 157.9, 180.6; IR (KBr): 4215, 3354, 3053, 3020, 2928, 2399, 1653, 1606, 1540, 1514, 1480, 1425, 1265, 1217, 1115, 928, 895, 766, 669 cm^{-1}; HRMS: calcd for $C_{32}H_{39}BrN_3O_6Si_2$ ([M+H]$^+$) 696.1561, found 696.1516.

4.1.10. Coscinamide A (1a). 9a (35.3 mg, 0.064 mmol) was converted to 23.2 mg (0.056 mmol, 89%) of coscinamide A (**1a**) according to the procedure described for the conversion of **9b** to coscinamide B (**1b**) as a yellow solid. Mp 240–243°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 6.82 (1H, d, J=15.0 Hz), 7.23 (1H, dd, J=1.8, 8.4 Hz), 7.25–7.29 (2H, m), 7.40 (1H, d, J=10.2, 15.0 Hz), 7.54 (1H, d, J=1.8 Hz), 7.55–7.57 (1H, m), 7.57 (1H, d, J=1.5 Hz), 7.62 (1H, d, J=8.7 Hz), 8.26–8.29 (1H, m), 8.83 (1H, brs), 10.56 (1H, d, J=10.2 Hz), 11.34 (1H, brs), 12.30 (1H, brs); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 109.2, 111.9, 112.3, 112.6, 114.3, 114.5, 119.3, 120.7, 121.3, 122.7, 123.6, 123.9, 125.1, 126.2, 136.3, 136.7, 138.7, 160.4, 181.1; IR (KBr): 4215, 3372, 3020, 2399, 2253, 1746, 1687, 1643, 1501, 1453, 1434, 1394, 1265, 1216, 1101, 1044, 934, 767 cm^{-1}; HRMS: calcd for $C_{20}H_{15}BrN_3O_4$ ([M+H]$^+$) 408.0348, found 408.0349.

4.1.11. *N*,*N*′,*N*″-tris-Teoc-chondriamide A (12). To a solution of **8b** (45.0 mg, 0.101 mmol) in THF (1 ml) was added a solution of NaHMDS (125 μl, 0.125 mmol, 1 M solution in THF) at 0°C for 10 min.On the other hand, to a solution of indole acrylic acid **7b** (43.4 mg, 0.131 mmol) in CH_2Cl_2 was added oxalyl chloride (19.4 μl, 0.223 mmol). After stirring at 25°C for 1 h, the solvent and excess of reagent were removed under vacuum to give the crude acid chloride.

The resulting crude acid chloride in THF (3 ml) was added to the previous mixture at 0°C via cannula. After stirring at 25°C for 2 h, the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried (Na_2SO_4) and evaporated in vacuo. The residue was purified by PTLC (hexane/EtOAc=8:1) to yield 62.8 mg (0.083 mmol, 82%) of *N*,*N*′,*N*″-tris-Teoc-Chondriamide A **12** as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (9H, s), 0.11 (18H, s), 1.14–1.31 (6H, m), 4.44–4.62 (6H, m), 6.83 (1H, dd, J=14.7, 0.9 Hz), 7.33 (1H, d, J=14.7 Hz), 7.34 (1H, dd, J=7.5, 1.2 Hz), 7.35 (1H, dd, J=8.1, 0.9 Hz), 7.40 (1H, ddd, J=6.6, 1.65, 1.8 Hz), 7.45 (1H, dd, J=6.9, 1.2 Hz), 7.52 (1H, d, J=15.9 Hz), 7.81 (1H, brs), 7.87 (1H, dd, J=7.5, 0.9 Hz), 7.94 (1H, dd, J=15.6, 0.6 Hz), 8.01 (1H, dd, J=7.2, 0.9 Hz), 8.19 (1H, brs), 8.25 (1H, brs), 8.25 (1H, dd, J=16.2, 1.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.7, −1.6, 17.8, 18.0, 66.4, 66.8, 66.9, 115.9, 116.1, 116.2, 118.0, 118.2, 120.8, 121.1, 121.2, 123.9, 124.1, 124.5, 125.5, 125.6, 126.0, 128.4, 129.1, 130.3, 136.3, 136.7, 137.1, 144.9, 150.6, 154.4, 168.0; IR (neat): 3054, 2954, 1738, 1617, 1551, 1455, 1392, 1356, 1308, 1232, 1094, 1059, 937, 860, 838, 761, 745cmcm^{-1}; HRMS: calcd for $C_{39}H_{53}N_3O_7Si_3$ ([M+H]$^+$) 760.3271, found 760.3289.

4.1.12. Chondriamide A (2). To a solution of *N*,*N*′,*N*″-tris-Teoc-Chondriamide A **12** (20 mg, 0.026 mmol) in THF (1.0 ml) was added a solution of TBAF (95 μl, 1 M solution in THF, 0.095 mmol) at 0°C. After the mixture was stirred at 0°C for 30 min, deposition was recrystallized by methanol and EtOAc to afford 9.8 mg (0.030 mmol, 92%) of chondriamide A (**2**) as a yellow solid. Mp 235–238°C; ^{1}H NMR (acetone-d_6, 300 MHz): δ 6.45 (1H, d, J=14.7 Hz), 6.77 (1H, d, J=15.6 Hz), 7.11 (2H, m), 7.19 (2H, m), 7.38 (1H, brs), 7.40 (1H, dd, J=7.8, 1.4 Hz), 7.50 (1H, dd, J=6.9, 1.5 Hz), 7.70 (1H, dd, J=14.7, 9.9 Hz), 7.76 (1H, brs), 7.76 (1H, dd, J=7.5, 2.1 Hz), 7.89 (1H, d, J=15.6 Hz), 7.96 (1H, dd, J=6.6, 2.4 Hz), 9.37 (1H, d, J=9.9 Hz), 10.3 (1H, brs), 10.8 (1H, brs); ^{13}C NMR (acetone-d_6, 75 MHz): δ 105.6, 112.2, 112.7, 113.6, 113.7, 116.1, 119.9, 119.9, 120.7, 121.2, 121.5, 122.2, 123.1, 123.2, 126.0, 126.1, 130.7, 135.3, 137.9, 138.4, 164.1; IR (neat): 3417, 3199, 3053, 1635, 1587, 1421, 1363, 1277, 1240, 1105, 1005, 943, 743 cm^{-1}; HRMS: calcd for $C_{21}H_{17}N_3O$ (M^+) 327.1372, found 327.1332.

4.1.13. 2-Trimethylsilylethyl *N*-[(*Z*)-2-{[(2-trimethylsilylethoxy)carbonyl]indolyl}-3-ethenyl]carbamate (13). A solution of (*E*)-carbamate **8b** (0.95 g, 2.1 mmol) in EtOAc (10 ml) was irradiated by a high-pressure mercury arc lamp for 1 h. After the solvent was removed under vacuum, the resulting residue was chromatographed on silica gel by eluting with 7% EtOAc in hexane to afford 0.14 g (0.32 mmol, 15%) of **13** and 0.72 g (1.6 mmol, 79%) of recovered **8b** as a yellow oil; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.03 (9H, s), 0.09 (9H, s), 0.95–1.03 (2H, m), 1.20–1.26 (2H, m), 4.23–4.25 (2H, m), 4.50–4.55 (2H, m), 5.64 (1H, d, J=8.71 Hz), 6.70 (1H, d, J=10.8 Hz), 6.84 (1H, dd, J=10.3, 9.1 Hz), 7.27–7.38 (2H, m), 7.52 (1H, d, J=7.81 Hz), 7.57 (1H, s), 8.18 (1H, d, J=8.1 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.5,-1.2, 17.6, 17.7, 64.0, 65.9, 97.4, 115.3, 116.1, 119.3, 121.9, 123.1, 124.9, 125.1, 129.6, 135.1, 150.9, 153.8; IR (neat): 3426, 3341, 3054, 2954, 2900, 1732, 1660, 1559, 1494, 1455, 1394, 1356, 1315, 1251, 1071, 935, 838, 748, 696 cm^{-1}; HRMS: calcd for $C_{22}H_{34}N_2O_4Si_2$ ([M+H]$^+$) 446.2057, found 446.2049.

4.1.14. *N*,*N*′,*N*″-tris-Teoc-Chondriamide C (14). (*Z*)-Carbamate **13** (45 mg, 0.10 mmol) was converted to

61 mg (0.080 mmol, 79%) of *N*,*N*′,*N*″-tris-Teoc-chondriamide C (**14**) as a yellow oil according to the procedure described for the conversion of **8b** to *N*,*N*′,*N*″-tris-Teoc-chondriamide A (**12**); ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.05 (27H, brs), 0.80–0.86 (2H, m), 1.01–1.02 (2H, m), 1.26–1.32 (2H, m), 4.16–4.21 (2H, m), 4.38–4.43 (2H, m), 4.58–4.64 (2H, m), 6.50 (1H, d, *J*=8.7 Hz), 6.71 (1H, dd, *J*=8.4, 0.9 Hz), 7.27–7.48 (4H, m), 7.67 (1H, brs), 7.72 (1H, d, *J*=7.8 Hz), 7.79 (1H, d, *J*=15.6 Hz), 7.91 (1H, d, *J*=15.6 Hz), 8.03 (1H, dd, *J*=6.6, 1.2 Hz), 8.16 (1H, brs), 8.18 (1H, brs), 8.29 (1H, dd, *J*=7.5, 1.8 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz): δ −1.7,-1.6, −1.5, 17.7, 17.9, 18.1, 66.2, 66.4, 67.0, 115.7, 116.2, 116.3, 117.9, 118.4, 120.0, 120.7, 121.3, 123.8, 124.4, 124.7, 125.7, 126.2, 126.2, 128.5, 130.4, 130.5, 130.7, 136.7, 137.2, 151.1, 151.2, 154.4, 167.7; IR (neat): 3054, 2954, 2900, 1733, 1683, 1615, 1556, 1455, 1392, 1356, 1250, 1094 cm^{-1}; HRMS: calcd for $C_{39}H_{53}N_3O_7Si_3$ ([M+H]$^+$) 760.3271, found 760.3289.

4.1.15. Chondriamide C (3). *N*,*N*′,*N*″-tris-Teoc-Chondriamide C (**14**) (20 mg, 0.026 mmol) was converted to 4.9 mg (0.015 mmol, 57%) of chondriamide C as a yellow solid according to the procedure described for the conversion of *N*,*N*′,*N*″-tris-Teoc-chondriamide A (**12**) to chondriamide A. Mp 224–227°C; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.93 (1H, d, *J*=9.3 Hz), 6.95 (1H, d, *J*=15.6 Hz), 7.04–7.21 (5H, m), 7.42 (1H, dd, *J*=8.1, 0.9 Hz), 7.48 (1H, dd, *J*=7.8, 0.9 Hz), 7.61–7.63 (2H, m), 7.74 (1H, d, *J*=2.7 Hz), 7.92 (1H, d, *J*=15.6 Hz), 7.96 (1H, d, *J*=8.1 Hz), 8.77 (1H, d, *J*=10.2 Hz), 10.5 (1H, brs), 10.8 (1H, brs); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 101.9, 111.7, 112.2, 113.0, 114.1, 116.1, 119.5, 120.1, 121.2, 121.3, 121.4, 122.7, 123.4, 124.2, 126.2, 128.0, 131.0, 136.3, 137.1, 138.7, 165.3; IR (KBr): 3387, 3051, 2960, 2922, 1676, 1639, 1610, 1532, 1496, 1456, 1420, 1359, 1338, 1281, 1245, 1230, 1185, 1101, 976 cm^{-1}; HRMS: calcd for $C_{21}H_{17}N_3O$ (M^+) 327.1372, found 327.1336.

4.1.16. 2-Trimethylsilylethyl *N*-[(*Z*)-2-{[(2-trimethylsilylethoxy)carbonyl]-6-bromoindole}-3-ethenyl]carbamate (15). A solution of (*E*)-carbamate **8a** (1.2 g, 2.6 mmol) in EtOAc (10 ml) was irradiated by a high-pressure mercury arc lamp for 1 h. After the solvent was removed under vacuum, the resulting residue was chromatographed on silica gel by eluting with 7% EtOAc in hexane to afford 0.17 g (0.38 mmol, 15%) of **15** and 0.96 g (2.2 mmol, 84%) of recovered **8a** as a yellow oil; ^{1}H NMR (benzene-d_6, 300 MHz): δ −0.10 (9H, s), 0.84–0.90 (4H, m), 4.16–4.22 (4H, m), 5.36 (1H, d, *J*=9.3 Hz), 6.92 (1H, m), 7.09 (1H, d, *J*=8.4 Hz), 7.29 (1H, dd, *J*=8.4, 1.5 Hz), 7.46 (1H, brs), 8.65 (1H, brs); ^{13}C NMR (benzene-d_6, 75 MHz): δ −1.7, −1.6, 17.5, 17.8, 64.0, 66.1, 96.8, 116.3, 118.8, 119.3, 121.0, 122.5, 125.8, 126.5, 128.9, 136.2, 150.4, 153.8; IR (neat): 3423, 3345, 3113, 2955, 1731, 1663, 1552, 1490, 1393, 1357, 1219, 1054, 945, 859, 764, 696 cm^{-1}; HRMS: calcd for $C_{22}H_{34}{}^{81}BrN_2O_4Si_2$ ([M+H]$^+$) 527.1220, found 527.1212.

4.1.17. *N*-[*Z*-{1-[(2-Trimethylsilyl)ethoxycarbonyl]-6-bromoindole}]-3-ethenyl]-α-methoxyoxoacetamide (16). To a solution of **15** (55 mg, 0.11 mmol) in THF (2 ml) was added a solution of NaHMDS (1 M solution in THF, 126 μl, 0.13 mmol) at 0°C for 10 min. Then methyl chloro acetate (14 mg, 0.15 mmol) was added to the mixture at 0°C. The mixture was stirred at room temperature for 1 h. Then the reaction was quenched by adding H_2O and the resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo.

To a solution of the resulting residue (67 mg) in THF (4 ml) was added a solution of TBAF (120 μl, 1 M solution in THF, 0.12 mmol) at 0°C. After the mixture was stirred at room temperature for 30 min, the reaction was quenched by adding H_2O. The resulting mixture was diluted with EtOAc. The layers were separated, the organic layer was washed with brine, dried ($MgSO_4$) and evaporated in vacuo. The residue was purified by PTLC (hexane/EtOAc=1:1) to yield 22.1 mg (0.07 mmol, 63%) of **16**; ^{1}H NMR (acetone-d_6, 300 MHz): δ 3.85 (3H, s), 6.19 (1H, d, *J*=9.0 Hz), 6.82 (1H, dd, *J*=9.0, 11.1 Hz), 7.24 (1H, dd, *J*=1.8, 8.4 Hz), 7.58–7.61 (2H, m), 7.68 (1H, d, *J*=1.2 Hz), 9.17 (1H, d, *J*=11.1 Hz), 10.97 (1H, brs); IR (neat): 4214, 3467, 3380, 3020, 2960, 2396, 1701, 1553, 1499, 1442, 1291, 1216, 1102, 1043, 769, 669 cm^{-1}; HRMS: calcd for $C_{13}H_{12}{}^{81}BrO_3N_2$ ([M+H]$^+$) 325.0010, found 325.0019.

4.1.18. Igzamide (4). After a solution of **16** (4.8 mg, 0.015 mmol) in MeOH-NH_3 (2 ml, 1:1) was stirred at 0°C for 30 min, the solvent was removed under reduced pressure. The resulting residue was purified by PTLC (hexane/EtOAc=2:1) to yield 4.6 mg (0.015 mmol, quant.) of igzamide (**4**) as a yellow solid. Mp 186–190°C; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 6.15 (1H, d, *J*=9.0 Hz), 6.69 (1H, dd, *J*=9.0, 11.0 Hz), 7.18 (1H, dd, *J*=1.8, 8.4 Hz), 7.54 (1H, s), 7.56 (1H, d, *J*=8.4 Hz), 7.61 (1H, d, *J*=1.8 Hz), 8.08 (1H, brs), 8.39 (1H, brs), 9.47 (1H, d, *J*=11.1 Hz), 11.55 (1H, brs); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 105.3, 109.3, 114.3, 118.0, 120.4, 122.3, 124.4, 125.3, 136.7, 157.2, 161.4; IR (KBr): 4209, 3395, 3021, 1665, 1609, 1525, 1384, 1217, 1117, 768, 670 cm^{-1}; HRMS: calcd for $C_{12}H_{11}{}^{81}BrO_2N_3$ ([M+H]$^+$) 310.0014, found 309.9995.

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