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# SYNTHESIS OF BREVICOMPANINES, PLANT GROWTH REGULATORS

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***Abstract*** —Brevicompanine A (**1)** and B (**2)** are plant growth regulators isolated from *Penicillium brevicompactum*. The synthesis of brevicompanine A (**1**) and B (**2**) was accomplished *via* a known intermediate.

## INTRODUCTION

Brevicompanine A (**1**) and B (**2**) were isolated from *Penicillium brevicompactum* as plant growth regulators by Kimura and coworkers in 1999.[1] Their activity as a plant growth regulator was examined using bioassay with lettuce and rice seedlings. With the lettuce seedling, both **1** and **2** showed inhibitory activities toward the hypocotyl elongation of seedlings at a concentration of 100 mg·l$^{-1}$. Although **1** accelerated the root growth of the seedlings in proportion to its concentration from 10 mg·l$^{-1}$ to 300 mg·l$^{-1}$, **2** promoted it less weakly than **1** in proportion to its concentration from 10 mg·l$^{-1}$ to 300 mg·l$^{-1}$. Both **l** and **2** showed no inhibitory effect on the root and stem elongation of rice seedlings at a concentration of 300 mg·l$^{-1}$. These molecules have a hexahydropyrrolo[2,3-*b*]indole (physostigmine) skeleton substituted with an inverted prenyl group and a diketopiperazine ring. Similar compounds such as Amauromine,[2] Fructigenine A[3] were isolated with various activities. Brevicompanine A (**1**) and B (**2**) consist of an L-tryptophan moiety and a D-leucine or D-*allo*isoleucine moiety. The presence of a D-amino acid in these molecules of **1** and **2** has not been reported among alkaloids with a similar skeleton. Therefore, brevicompanines are of considerable interest to us, because of the relationship of the structural uniqueness and the biological activity, and so, we tried to synthesize brevicompanie A (**1**), B (**2**) and their isomer, *allo*brevicompanines (**3**, **4)**.

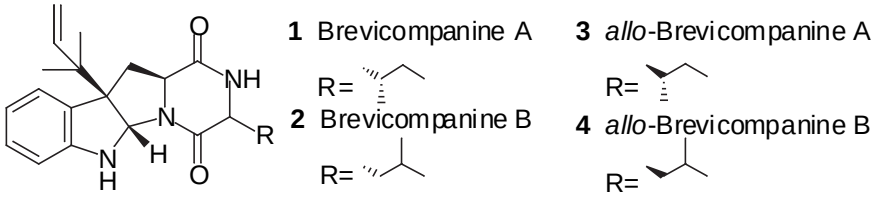
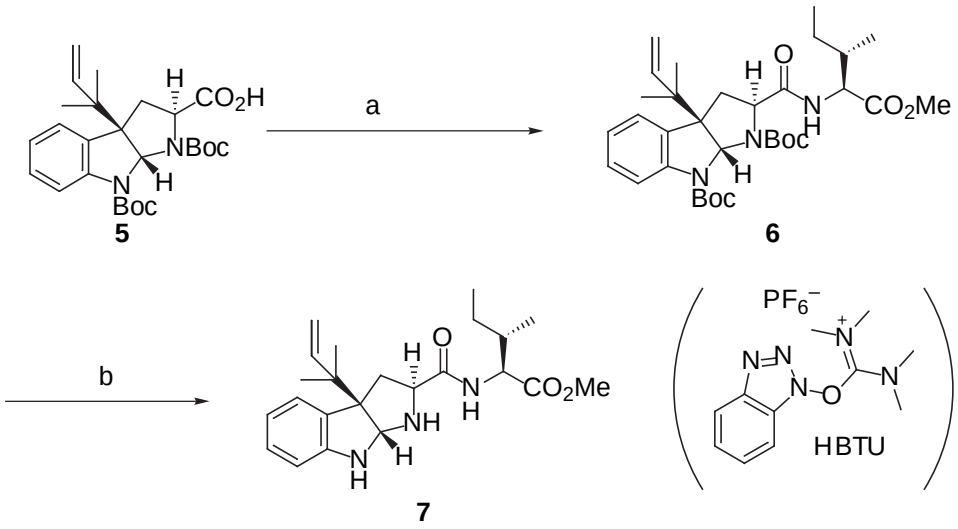



**Figure 1.**

† Dedicated to Professor Sho Ito on the occasion of his 77th birthday.

## RESULTS AND DISCUSSION

Among the breivicompanines, we first tried to synthesize *allo*-brevicompanine A (**3**), which can be synthesized from L-isoleucine, to establish the synthetic route. The carboxylic acid (**5**), obtained according to the Danishefsky's procedure,[4] was condensed with L-isoleucine methyl ester hydrochloride by using HBTU (*O*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate) as condensing agent and *N*-ethylmorpholine in methylene chloride to give **6** in 81% yield. Other condensing reagents (i.e., DCC, BOP-Cl, and BOP) did not give any better results. This amide was treated with TMSOTf (trimethylsilyl trifluoromethanesulfonate) in methylene chloride at –15°C to give free diamine (**7**) in 82% yield.



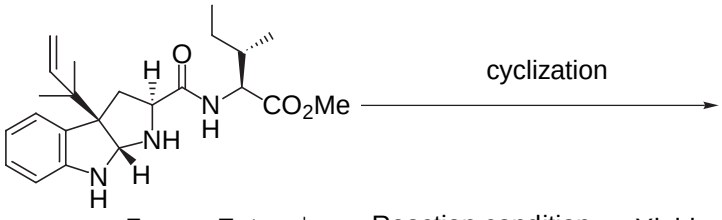

**Scheme 1.** a) L-Ile-OMe·HCl, *N*-ethylmorpholine, HBTU, $CH_2Cl_2$. b) TMSOTf, $CH_2Cl_2$.

The final step, construction of the diketopiperazine ring, was initially examined by using saturated ammonia in methanol, which was used in the synthesis of related diketopiperazine. However, cyclization did not occur in our case probably because of the bulkiness of the branched amino acid (Table1). We next used NaCN which catalyzes the condensation of primary or secondary amine and ester.[5] Thus, we used a catalytic amount in methanol under reflux for 3 days and obtained the desired compound (**3**), but the prolonged refluxing caused the decomposition of the starting material and the yield was very poor (13%). When we used excess amount of NaCN, the reaction rate was accelerated (overnight) and the yield was improved, but not enough (38%). So, a diketopiperazine ring was constructed in two steps, hydrolysis of the methyl ester and intramolecular condensation of the resulting aminocarboxylic acid. The diamine (**7**) was hydrolyzed with a solution of 0.5N LiOH in tetrahydrofuran-methanol and the crude product was condensed directly with HBTU in methylene chloride to give *allo*-brevicompanine A in good yield (70% in 2 steps). Thus, the synthetic route was established. We succeeded in the synthesis of brevicompanine A by the same route as that of *allo*-brevicompanine A using D-*allo*-isoleucine methyl ester hydrochloride. The $^1$H-NMR, $^{13}$C-NMR, and IR data of our synthetic **1** were identical with those of natural **1**. The overall

yield is 12.2% in 9 steps from L-tryptophan. We also synthesized brevivompanine B (**2**) and *allo*-brevicompanine B (**4**) from D-leucine and L-leucine in total 11.0% and 9.2% yield. The $^{1}$H-NMR, $^{13}$C-NMR, and IR data of our synthetic **2** were also identical with those of natural **2**. Biological studies and investigation of the structure and activity relationship by using the synthesized brevicompanines are now in progress.

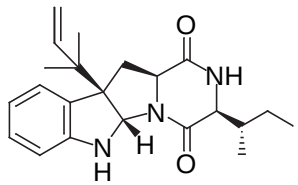
**Table 1.**

In conclusion, we have synthesized brevicompanine A, B and their analog *allo*-brevicompanine A and B in 9 steps from L-tryptophan and the total yields were 9.2 ~ 12.2%.




**7**

| Entry | Reaction condition | Yield |
|---|---|---|
| 1 | $NH_3$, MeOH | no reaction |
| 2 | $NH_3$, DMAP, MeOH | no reaction |
| 3 | NaCN (0.2 eq.) MeOH, reflux, 3 days | 13% |
| 4 | NaCN (6 eq.) MeOH, reflux, overnight | 38% |
| 5 | i) 0.5N LiOH, THF-MeOH, rt ii) HBTU, $CH_2Cl_2$ | 70% |



**3**
*allo*-Brevicompanine A
(total 10 steps, 11%)

## EXPERIMENTAL

Melting points dates were recorded on a Yamaco MP-S3 melting point apparatus and are uncorrected. IR were recorded with a Jasco FT/IR-230 spectrometer and are reported in wave number (cm $^{-1}$). $^{1}$H-NMR spectra were recorded with a JEOL JNM-AL300 spectrometer (300 MHz) or JEOL Alpha-600 spectrometer (600 MHz), and $^{13}$C NMR spectra were recorded with JEOL Alpha-600 spectrometer (125 MHz). HRFABMS were recorded with a JEOL JMS-SX102/102. Refractive indices were recorded with a Jasco DIP-1000. Column chromatography: Merck Kieselgel F-254. Neutral column chromatography: Kanto Chemical Silica Gel 60N (spherical, neutral).

*(2S,3aR,8aR)-1,8-Bis-t-butoxycarbonyl-2-methoxycarbonyl-3a-phenylseleno-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indole* (**5**)
mp102.0~102.58°C (from Hexane - EtOAc), $[\alpha]_D^{20}$= –57.4° (*c* 0.25, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3461 (b), 2977 (s), 1716 (s), 1602 (w), 1480 (m), 1396 (s), 1367 (s), 1278 (m), 1256 (m), 1220 (m), 1161 (s), 1088 (w), 1020 (m), 921 (w), 853 (w), 794 (w), 754 (m)
$^{1}$H NMR(300 MHz, $CDCl_3$): δ = 7.31~7.06 (m, 2H), 7.17 (d, 1H, *J* = 7.5 Hz), 7.05 (t, 1H, *J* = 7.5 Hz),

6.15 (s, 1H), 5.86 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (d, 1H, *J* = 11 Hz), 5.01 (d, 1H, *J* = 17 Hz), 2.83 (dd, 1H, *J* = 6.6 Hz, *J* = 10 Hz, H-2), 2.44 (dd, 1H, *J* = 12 Hz, *J* = 6.6 Hz, H-3), 2.36 (dd,1H, *J* = 12 Hz, *J* = 10 Hz), 1.55 (s, 9H), 1.43 (br s, 9H), 1.03 (s, 3H), 0.94 (s, 3H)

*Methyl (2S,3S)-2-[{(2S,3aS,8aR)-1,8-bis-t-butoxycarbonyl-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-3-methylpentanoate* (**6**)
To a mixture of **5** (0.37 g, 0.78 mmol) and L-isoleucine methyl ester hydrochloride (0.17 g, 0.94 mmol) in $CH_2Cl_2$ (10 mL) was added *N*-ethylmorpholine (0.11 g, 0.94 mmol) under argon at –10°C and stirred for 10 min. To this was added HBTU (0.30 g, .78 mmol) and the mixture was stirred for 14 h at rt. The reaction mixture was cooled to 0°C, diluted with sat. $NaHCO_3$ solution, and extracted with $CHCl_3$. The extract was washed with water and brine, dried with $Na_2SO_4$, and concentrated. The oily residue was chromatographed by column (neutral silica gel, Hexane : EtOAc = 10 : 1) furnishing pure **6** as an oil (0.38 g, 81%): $[\alpha]_D^{22}$= –62.0° (*c* 0.15, $CHCl_3$); IR(film):$\nu_{max}$($cm^{-1}$)= 2974 (m), 1712 (s), 1515 (m), 1480 (s), 1392 (s), 1366 (s), 1255 (m), 1157 (s), 1063 (w), 916 (m), 856 (m), 753 (s), 688 (w), 664 (w); $^1$H NMR(300 MHz, $CDCl_3$): δ =7.24 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 1H, *J* = 7.5 Hz), 7.06 (t, 1H, *J* = 7.2 Hz), 6.18 (d, 1H, *J* = 7.5 Hz), 6.16 (s, 1H), 5.87 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (d, 1H, *J* = 11 Hz), 5.01 (d, 1H, *J* = 17 Hz), 4.68 (dd, 1H, *J* = 7.2 Hz, *J* = 10 Hz), 3.75 (dd, 1H, *J* = 7.2 Hz, *J* = 10 Hz), 3.73 (s, 3H), 2.45 (dd, 1H, *J* = 13 Hz, *J* = 7.2 Hz), 2.32 (dd, 1H, *J* = 13 Hz, *J* = 10 Hz), 2.03~1.84 (m, 1H), 1.55 (s, 9H), 1.41 (br s, 9H), 1.71~1.31 (m, 2H), 1.04 (s, 3H), 0.96 (s, 3H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.83 (d, 3H, *J* = 6.9 Hz); HRFABMS m/z 600.7654 (Calcd 600.7661) $C_{33}H_{50}N_3O_7$

*Methyl (2S,3S)-2-[{(2S,3aS,8aR)-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-3-methylpentanoate* (**7**)
To a solution of **6** (0.30 g, 0.50 mmol) in $CH_2Cl_2$ (30 mL) was added TMSOTf (1.1 g, 5.0 mmol) under argon at –30°C and the mixture was stirred for 1.5 h at –15°C. The reaction mixture was diluted with sat. $NaHCO_3$ solution and extracted with $CHCl_3$. The extract was washed with water and brine, dried with $Na_2SO_4$, and concentrated. The oily residue was chromatographed by column (neutral silica gel, $CHCl_3$) furnishing pure **7** as an oil (0.16 g, 82%): $[\alpha]_D^{22}$= –95.9° (*c* 1.30, $CHCl_3$); IR(film):$\nu_{max}$($cm^{-1}$)= 3333 (m), 2966 (s), 1745 (s), 1681 (m), 1605 (m), 1485 (s), 1205 (s), 1006 (m), 916 (m), 753 (s); $^1$H NMR(300 MHz, $CDCl_3$): 7.13 (d, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.74 (t, 1H, *J* = 7.5 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 5.97 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (d, 1H, *J* = 11 Hz), 5.03 (s,1H), 5.03 (d, 1H, *J* = 17 Hz), 4.56 (dd, 1H, *J* = 9.0 Hz, *J* = 5.1 Hz), 3.72 (s, 3H), 3.56 (dd, 1H, *J* = 9.9 Hz, *J* = 6.0 Hz), 2.33 (dd, 1H, *J* = 12 Hz, *J* = 6.0 Hz), 2.13 (dd, 1H, *J* = 12 Hz, *J* = 9.9 Hz), 1.95~1.84 (m, 1H), 1.49~1.42 (m, 1H), 1.15~1.03 (m, 1H), 1.09 (s, 3H), 0.99 (s, 3H), 0.93 (d, 3H), 0.91 (d, 3H, *J* = 7.6 Hz); HRFABMS m/z 400.5441 (Calcd 400.5345) $C_{23}H_{34}N_3O_3$

*(2S,10aS,5aS,4aS)-5a-(1,1-Dimethylprop-2-enyl)-2-{(S)-methylpropyl}1,2,3,4,4a,5,5a,10a-octahydro-10H-pyrazino[1',2':1,2]pyrrolo[4,5-b]indole-1,4-dione* (*allo*-brevicompanine A) (**3**)
To a solution of **7** (0.0090 g, 0.0023 mmol) in THF-MeOH (3 :1) (2 mL) was added 0.5N LiOH solution (0.010 mL, 0.0050 mmol) at 0°C. The mixture was stirred for 3 h at rt. The reaction mixture was added to 1N $KHSO_4$ solution (0.010 mL, 0.010 mmol) and diluted with sat. $(NH_4)_2SO_4$ solution, extracted with $CHCl_3$. The extract was dried with $Na_2SO_4$ and concentrated. A solution of crude acid in $CH_2Cl_2$ (2 mL) was added HBTU (0.010 g, 0.027 mmol) under argon at –10°C. The mixture was stirred for 14 h at rt. The reaction mixture was cooled to 0°C and diluted with sat. $NaHCO_3$ solution, extracted with $CHCl_3$. The extract was washed with water and brine, dried with $Na_2SO_4$, and concentrated. The oily residue was chromatographed by column (neutral silica gel, $CHCl_3$) furnishing pure **3** as an oil (0.0061 g, 73% in 2 steps): $[\alpha]_D^{22}$= –247.0° (*c* 2.32, $CHCl_3$); IR(film):$\nu_{max}$($cm^{-1}$)= 3733 (w), 3628 (w), 3323 (m), 2965 (m), 2876 (m), 1672 (s), 1606 (m), 1435 (m),1318 (m), 1215 (m), 1145 (w), 1097 (w), 914 (m), 735 (m), 669 (m); $^1$H NMR(300 MHz, $CDCl_3$): δ = 7.15 (d, 1H, *J* = 7.2 Hz), 7.09 (dd, 1H, *J* = 7.5 Hz, *J* = 7.8 Hz), 6.75 (dd, 1H, *J* = 7.5 Hz, *J* = 7.2 Hz), 6.57 (d, 1H, *J* = 7.8 Hz), 5.95 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.84 (s, 1H), 5.55 (s, 1H), 5.11 (d,1H, *J* = 11 Hz), 5.08 (d,1H, *J* = 17 Hz), 3.94 (m, 2H), 2.53 (dd, 1H, *J* = 12 Hz, *J* = 6.0 Hz), 2.41 (dd, 1H, *J* = 12 Hz, *J* = 11 Hz), 2.29 (m, 1H), 1.60~1.11 (m, 2H), 1.12 (s, 3H), 1.02 (d, 3H, *J* = 7.2 Hz), 1.01 (s, 3H), 0.91 (t, 3H, *J* = 7.2 Hz) HRFABMS m/z 367.2271 (Calcd 367.2260) $C_{22}H_{29}N_3O_2$

In the same manner as above, brevicompanine A (0.25 g, 51%) was obtained from **5.**

*Methyl (2R,3S)-2-[{(2S,3aS,8aR)-1,8-bis-t-butoxycarbonyl-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-3-methylpentanoate*
$[\alpha]_D^{22}$= –65.5° (*c* 0.30, $CHCl_3$), IR(film):$\nu_{max}$($cm^{-1}$)= 2974 (m), 1712 (s), 1515 (m), 1480 (s), 1392 (s), 1366 (s), 1255 (m), 1157 (s), 1063 (w), 916 (m), 856 (m), 753 (s), 688 (w), 664 (w)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.24 (t, 1H, *J* = 7.2 Hz), 7.18 (d, 1H, *J* = 7.5 Hz), 7.06 (t, 1H, *J* = 7.2 Hz), 6.18 (d, 1H, *J* = 7.5 Hz), 6.16 (s, 1H), 5.87 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (d, 1H, *J* = 11 Hz), 5.01 (d, 1H, *J* = 17 Hz), 4.68 (dd, 1H, *J* = 7.2 Hz, *J* = 10 Hz), 3.75 (dd, 1H, *J* = 7.2 Hz, *J* = 10 Hz), 3.73 (s, 3H), 2.45 (dd, 1H, *J* = 13 Hz, *J* = 7.2 Hz), 2.32 (dd, 1H, *J* = 13 Hz, *J* = 10 Hz), 2.03~1.84 (m, 1H), 1.55 (s, 9H), 1.41 (br s, 9H), 1.71~1.31 (m, 2H), 1.04 (s, 3H), 0.96 (s, 3H), 0.91 (t, 3H, *J* = 7.2 Hz), 0.83 (d, 3H, *J* = 6.9 Hz)

*Methyl (R)-2-[{(2S,3aS,8aR)-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-4-methylpentanoate*
$[\alpha]_D^{22}$= –89.8° (*c* 1.62, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3725 (w), 3628 (w), 3331(w), 2958 (m), 1746 (s), 1661 (s), 1605 (w), 1518 (m), 1484 (m), 1470 (m), 1259 (m), 1201 (m), 1156 (m), 1024 (w), 914 (w), 742 (m), 669 (s)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.13 (d, 1H, *J* = 7.5 Hz), 7.06 (t, 1H, *J* = 7.5 Hz), 6.74 (t, 1H, *J* = 7.5 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 5.97 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.06 (d, 1H, *J* = 11 Hz), 5.02 (d, 1H, *J* = 17 Hz), 4.99 (s, 1H), 4.62~4.54 (m, 1H), 3.72 (s, 3H), 3.56 (dd, 1H, *J* = 10 Hz, *J* = 6.0 Hz), 2.29 (dd, 1H, *J* = 12 Hz, *J* = 6.0 Hz), 2.20 (dd, 1H, *J* = 12 Hz, *J* = 10 Hz), 1.67~1.57 (m, 3H), 1.08 (s, 3H), 1.01 (s, 3H), 0.93 (t, 3H, *J* =3.6 Hz), 0.91 (d, 3H, *J* = 3.3 Hz)

*(2R,10aS,5aS,4aS)-5a-(1,1-Dimethylprop-2-enyl)-2-{(S)-methylpropyl}-1,2,3,4,4a,5,5a,10a-octahydro-10H-pyrazino[1',2':1,2]pyrrolo[4,5-b]indole-1,4-dione* (brevicompanine A) (**1**)
$[\alpha]_D^{22}$= –212.6° (*c* 0.12, EtOH), *natural*[1] $[\alpha]_D^{20}$= –237.5° (*c* 0.73, EtOH)
IR(film):$\nu_{max}$($cm^{-1}$)= 3733 (w), 3628 (w), 3323 (m), 2965 (m), 2876 (m), 1672 (s), 1606 (m), 1435 (m), 1318 (m), 1215 (m), 1145 (w), 1097 (w), 914 (m), 735 (m), 669 (m)
$^1$H NMR(600 MHz, $CDCl_3$): δ = 7.15 (d, 1H, *J* = 7.7 Hz), 7.09 (t, 1H, *J* = 7.4 Hz), 6.75 (dd, 1H, *J* = 7.7 Hz, *J* = 7.3 Hz), 6.58 (d, 1H, *J* = 7.7 Hz), 6.30 (s, 1H), 5.96 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.58 (s, 1H), 5.55 (s, 1H), 5.12 (d,1H, *J* = 11 Hz), 5.08 (d,1H, *J* = 17 Hz), 3.91 (m, 2H), 2.54 (dd, 1H, *J* = 12 Hz, *J* = 5.7 Hz), 2.37 (dd, 1H, *J* = 12 Hz, *J* = 11 Hz), 2.00 (m, 1H), 1.44~1.16 (m, 2H), 1.11 (s, 3H), 1.00 (s, 3H), 0.91 (t, 3H, *J* = 7.3 Hz), 0.76 (d, 3H, *J* = 6.9 Hz)
$^{13}$C NMR(150 MHz, $CDCl_3$): δ = 169.2, 165.9, 150.0, 143.5, 129.0, 128.7, 125.1, 118.8, 114.5, 108.8, 77.6, 61.1, 57.9, 40.9, 39.8, 37.0, 25.8, 22.9, 22.4, 13.8, 11.5
HRFABMS m/z 367.2263 (Calcd 367.2260) $C_{22}H_{29}N_3O_2$

In the same manner as above, brevicompanine B (0.054 g, 43%) was obtained from **5.**

*Methyl (R)-2-[{(2S,3aS,8aR)-1,8-bis-t-butoxycarbonyl-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-4-methylpentanoate*
$[\alpha]_D^{22}$= –74.6°(*c* 0.26, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3361 (w), 2974 (m), 1714 (s), 1610 (w), 1538 (m), 1480 (m), 1392 (s), 1158 (s), 1021 (m), 918 (m), 858 (m), 753 (s), 666 (w)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.22 (dd, 1H, *J* = 7.2 Hz, *J* = 7.5 Hz), 7.18 (d, 1H, *J* = 7.5 Hz), 7.06 (d, 1H, *J* = 7.2 Hz, *J* = 7.5 Hz), 7.05 (d, 1H, *J* = 7.5 Hz), 6.15 (s, 1H), 6.05 (d, 1H, *J* = 9.0 Hz) 5.87 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (dd,1H, *J* = 11 Hz, *J* =0.9 Hz), 5.01 (d, 1H, *J* = 17 Hz, *J* = 0.9 Hz), 4.66~4.58 (m, 1H), 3.67~3.74 (m, 1H), 3.72 (s, 3H), 2.45 (dd, 1H, *J* = 13 Hz, *J* = 11 Hz), 2.34 (dd, 1H, *J* = 13 Hz, *J* = 6.9 Hz), 1.68~1.60 (m, 3H), 1.56 (s, 9H), 1.40 (br s, 9H), 1.04 (s, 3H), 0.96 (s, 3H), 0.92 (d, 3H, *J* = 5.7 Hz), 0.91 (d, 3H, *J* = 6.3 Hz)

*Methyl (R)-2-[{(2S,3aS,8aR)-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-4-methylpentanoate*
$[\alpha]_D^{22}$= –89.8° (*c* 1.62, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3725 (w), 3628 (w), 3331 (w), 2958 (m), 1746 (s), 1661 (s), 1605 (w), 1518 (m), 1484 (m), 1470 (m), 1259 (m), 1201 (m), 1156 (m), 1024 (w), 914 (w), 742 (m), 669 (s)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.13 (d, 1H, *J* = 7.5 Hz), 7.06 (t, 1H, *J* = 7.5 Hz), 6.74 (t, 1H, *J* = 7.5 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 5.97 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.06 (d, 1H, *J* = 11 Hz), 5.02 (d, 1H,

*J* = 17 Hz), 4.99 (s, 1H), 4.62~4.54 (m, 1H), 3.72 (s, 3H), 3.56 (dd, 1H, *J* = 10 Hz, *J* = 6.0 Hz), 2.29 (dd, 1H, *J* = 12 Hz, *J* = 6.0 Hz), 2.20 (dd, 1H, *J* = 12 Hz, *J* = 10 Hz), 1.67~1.57 (m, 3H), 1.08 (s, 3H), 1.01 (s, 3H), 0.93 (t, 3H, *J* =3.6 Hz), 0.91 (d, 3H, *J* = 3.3 Hz)

*(2R,10aS,5aS,4aS)-5a-(1,1-Dimethylprop-2-enyl)-2-(2-methylpropyl)-1,2,3,4,4a,5,5a,10a-octahydro-10H-pyrazino[1',2':1,2]pyrrolo[4,5-b]indole-1,4-dione* (brevicompanine B) (**2**)
$[\alpha]_D^{22}$= –224.0° (*c* 0.63, EtOH), *natural* $^1[\alpha]_D^{20}$= –228.3° 0.46, EtOH)
IR(film):$\nu_{max}$($cm^{-1}$)= 3319 (w), 2958 (m), 1679 (s), 1607 (m) 1444 (w), 1382 (w), 1316 (w), 1214 (w), 1079 (w), 917 (w), 748 (m)
$^1$H NMR(600 MHz, $CDCl_3$): δ = 7.16 (d, 1H, *J* = 7.3 Hz), 7.10 (dd, 1H, *J* = 7.3 Hz, *J* = 7.8 Hz), 6.76 (dd, 1H, *J* = 7.8 Hz, *J* = 7.3 Hz), 6.59 (d, 1H, *J* = 7.8 Hz), 6.42 (s, 1H), 5.97 (dd, 1H, *J* = 18 Hz, *J* = 11 Hz,), 5.55 (s, 1H), 5.12 (d, 1H, *J* = 11 Hz), 5.07 (d, 1H, *J* = 18 Hz), 4.89 (s, 1H), 3.88 (m, 2H), 2.54 (dd, 1H, *J* = 13 Hz, *J* = 6.3 Hz), 2.46 (dd,1H, *J* = 13 Hz, *J* = 12 Hz), 1.84~1.42 (m, 3H), 1.12 (s, 3H), 1.00 (s, 3H), 0.91 (d, 3H, *J* = 6.8 Hz), 0.90 (d, 3H, *J* = 6.8 Hz)
$^{13}$C NMR(150 MHz, $CDCl_3$): δ = 169.2, 166.6, 150.0, 143.4, 128.9, 125.1, 118.8, 114.6, 109.1, 77.7, 61.2, 57.8, 42.8, 40.9, 36.6, 24.3, 23.0, 22.8, 22.4, 21.2
HRFABMS m/z 367.2275 (Calcd 367.2260) $C_{22}H_{29}N_3O_2$

In the same manner as above, *allo*-brevicompanine B (0.048 g, 38%) was obtained from **5.**

*Methyl (2S)-2-[{(2S,3aS,8aR)-1,8-bis-t-butoxycarbonyl-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-4-methylpentanoate*
$[\alpha]_D^{22}$= –52.4° (*c* 2.19, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 2974 (m), 1712 (s), 1515 (m), 1480 (s), 1392 (s), 1366 (s), 1255 (m), 1157 (s), 1063 (w), 916 (m), 856 (m), 753 (s), 688 (w), 664 (w)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.26~7.15 (m, 3H), 7.06 (t, 1H, *J* = 7.2 Hz), 6.14 (s, 1H), 6.06 (br.d,1H, *J* = 8.1 Hz), 5.87 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.06 (d, 1H, *J* = 11 Hz), 5.00 (d, 1H, *J* = 17 Hz), 4.64 (m, 1H), 3.71 (s, 3H), 3.65 (dd, 1H, *J* = 9.9 Hz, *J* = 6.9 Hz), 2.40~2.34 (m, 2H), 1.84~1.54 (m, 3H), 1.54 (s, 9H), 1.41 (br s, 9H), 1.03 (s, 3H), 0.93 (d, 3H, *J* = 4.8 Hz), 0.92 (s, 3H), 0.91 (d, 3H, *J* = 5.4 Hz)

*Methyl (S)-2-[{(2S,3aS,8aR)-3a-(1,1-dimethylprop-2-enyl)-1,2,3,3a,8,8a-hexahydropyrrolo[2,3-b]indol-2-yl}carbonylamino]-3-methylpentanoate*
$[\alpha]_D^{22}$= –91.3° (*c* 1.83, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3338 (m), 2957 (m), 1735 (m), 1654 (s), 1560 (m), 1541 (m), 1509 (m), 1458 (m) 1204 (m), 742 (s)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.13 (d, 1H, *J* = 7.5 Hz), 7.07 (t, 1H, *J* = 7.5 Hz), 6.75 (t, 1H, *J* = 7.5 Hz), 6.58 (d, 1H, *J* = 7.5 Hz), 5.96 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.08 (d, 1H, *J* = 11 Hz), 5.04 (s, 1H), 5.03 (d, 1H, *J* = 17 Hz), 4.62 (m, 1H), 3.71 (s, 3H), 2.57 (dd, 1H, *J* = 11 Hz, *J* = 6.0 Hz), 2.34 (dd, 1H, *J* = 6.0 Hz, *J* = 12 Hz,), 2.14 (dd, 1H, *J* = 12 Hz, *J* = 11 Hz), 1.68~1.52 (m, 3H), 1.09 (s, 3H), 0.93 (d, 3H, *J* = 7.2 Hz), 0.92 (s, 3H), 0.84 (d, 3H, *J* = 6.9 Hz)

*(2S,10aS,5aS,4aS)-5a-(1,1-Dimethylprop-2-enyl)-2-(2-methylpropyl)-1,2,3,4,4a,5,5a,10a-octahydro-10H-pyrazino[1',2':1,2]pyrrolo[4,5-b]indole-1,4-dione* (allo-brevicompanine B) (**4**)
$[\alpha]_D^{22}$= –258.0° (*c*0.67, $CHCl_3$)
IR(film):$\nu_{max}$($cm^{-1}$)= 3318 (w), 2959 (m), 1682 (s), 1559 (w), 1541 (w), 1508 (w), 1457 (m), 1419 (m), 1315 (w), 1213 (w), 1149 (w), 918 (w), 752 (m)
$^1$H NMR(300 MHz, $CDCl_3$): δ = 7.16 (d, 1H, *J* = 7.2 Hz), 7.10 (t, 1H, *J* = 7.5 Hz), 6.76 (t, 1H, *J* = 7.5 Hz), 6.58 (d, 1H, *J* = 7.5 Hz), 5.97 (dd, 1H, *J* = 17 Hz, *J* = 11 Hz), 5.87 (s, 1H), 5.50 (s, 1H), 5.12 (d, 1H, *J* = 11 Hz), 5.08 (d, 1H, *J* = 17 Hz), 3.96 (m, 2H), 2.54 (dd, 1H, *J* = 12 Hz, *J* = 6.6 Hz), 2.46 (dd,1H, *J* = 12 Hz, *J* = 11 Hz), 2.01 (m, 1H), 1.74~1.52 (m, 2H), 1.12 (s, 3H), 1.01 (s, 3H), 0.99 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 6.9 Hz)
HRFABMS m/z 367.2277 (Calcd 367.2260) $C_{22}H_{29}N_3O_2$

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**REFERENCES**

1 M. Kusano, G. Sotoma, H. Koshino, J. Uzawa, M. Chijimatsu, S. Fujioka, T. Kawano, and Y. Kimura, *J. Chem. Soc., Perkin Trans. 1,* 1998, 2823.

2 S. Takase, M. Iwami, T. Ando, M. Okamoto, K. Yoshida, H. Horiai, M. Kosaka, H. Aoki, and H. Imanaka, *J. Antibiot*., 1984, **41,** 3037.

3 K. Arai, K. Kimura, T. Mushiroda, Y. Yamamoto, *Chem. Pharm. Bull*., 1989, **37,** 2937.

4 S. P. Maraden, K. M. Depew, and S. J. Danishefsky, *J. Am. Chem. Soc*., 1994, **116,** 11143 and cited therein, K. M. Depew, S. P. Maraden, D. Zatorska, A. Zatorski, W. G. bornmann, and S. J. Danishefsky, *ibid.,* 1999, **121,** 11953.

5 T. Högberg, P. Ström, M. Ebner, and S. Rämsby, *J. Org. Chem.*, 1987, **52,** 2033.