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The first synthesis of (±)-brevione B, an allelopathic agent isolated from *Penicillium* sp.

Hirosato Takikawa,* Manabu Hirooka and Mitsuru Sasaki

Department of Biofunctional Chemistry, Kobe University, Rokkodai 1-1, Nada-ku, Kobe 657-8501, Japan

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Abstract—Breviones A∼E (**1**∼**5**), allelopathic agents isolated from *Penicillium brevicompactum* Dierckx, are structurally unique pentacyclic or hexacyclic diterpenoid derivatives. The first synthesis of brevione B (**2**) was achieved by employing the double S_N2'-type tandem reaction as a key step.

Allelopathy is commonly defined as any direct or indirect effect by one plant, including microorganisms, on another through the production of chemical compounds released into the environment. It includes both inhibitory and stimulative reciprocal biochemical interactions.[1] Nowadays, allelopathic agents have received a considerable amount of attention due to the agricultural potential of these compounds as environmentally-benign herbicides.[1] In 2000, Macías and co-workers isolated breviones A∼E (**1**∼**5**) from *Penicillium brevicompactum* Dierckx as allelopathic agents.[2] These compounds are structurally unique natural products consisting of diterpene and polyketide subunits. Especially, the spiro-fused CDE ring portion of breviones A∼D (**1**∼**4**) is characteristic and unusual. We became interested in the biological activities and the unique structures of breviones, and undertook a project to synthesize them. Herein, we report the first synthesis of (±)-brevione B (**2**) (Fig. 1).

Because a crucial point in the synthesis of breviones should be the construction of the characteristic spiro-fused CDE ring framework, we assigned a structurally simplified model compound (**6**) as the tentative target molecular. For the synthesis of **6**, the direct coupling of **7** and **8** by the double S_N2'-type tandem reaction was envisioned. This plan has been realized by a palladium-mediated tandem reaction as shown in Scheme 1.[3] The next challenge was the total synthesis of brevione B (**2**) employing the developed tandem reaction as a key step.

Our synthetic plan for **2** is illustrated in Scheme 1. The target compound **2** might be readily obtainable from **A**. For the preparation of **A**, we envisioned adopting our original tandem reaction, by which the direct coupling of **B** and **C** to **A** was possible.[3,4] The key intermediate, vinylepoxide **C**, should be prepared from the methylated Wieland–Miescher ketone **E** via the tricyclic ketone **D**.

Scheme 2 shows our synthetic route to the key intermediate **14**. First, we synthesized the known hydroxy ketone **10**[5] from **9**.[6] The hydroxy ketone **10** was then converted into **11** by the conventional three steps: catalytic hydrogenation (81%), protection of the carbonyl group (89%), and oxidation of the hydroxy group (92%). Methylation of the ketone **11** was performed by treatment with LDA and iodomethane to give methyl-

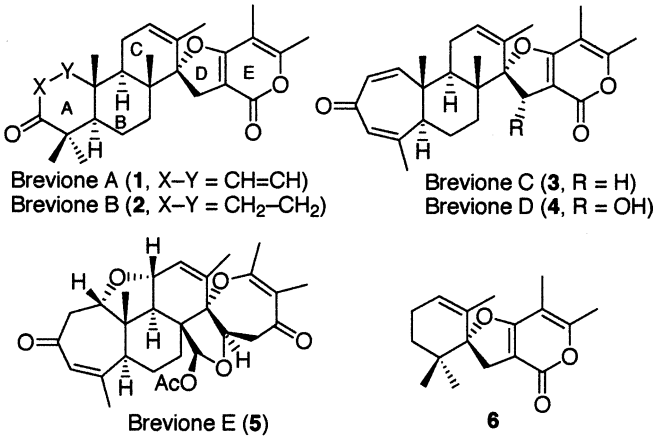

Figure 1. Structures of breviones.

Keywords: diterpenoids; α-pyrone; allelopathic agents; tandem reaction.

* Corresponding author. Tel./fax: +81-78-803-5958; e-mail: takikawa@ans.kobe-u.ac.jp

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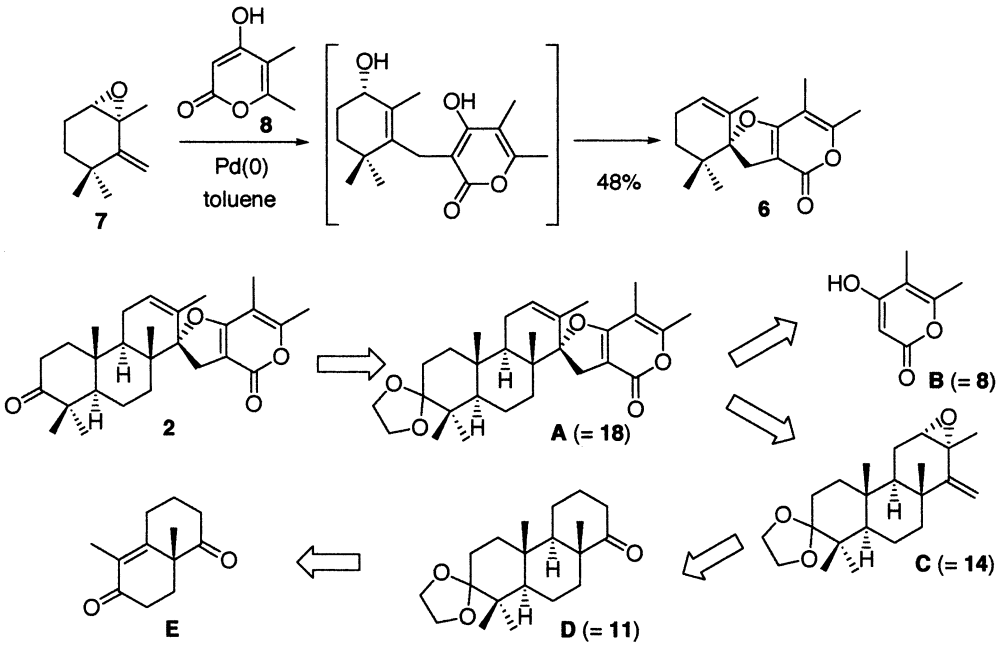
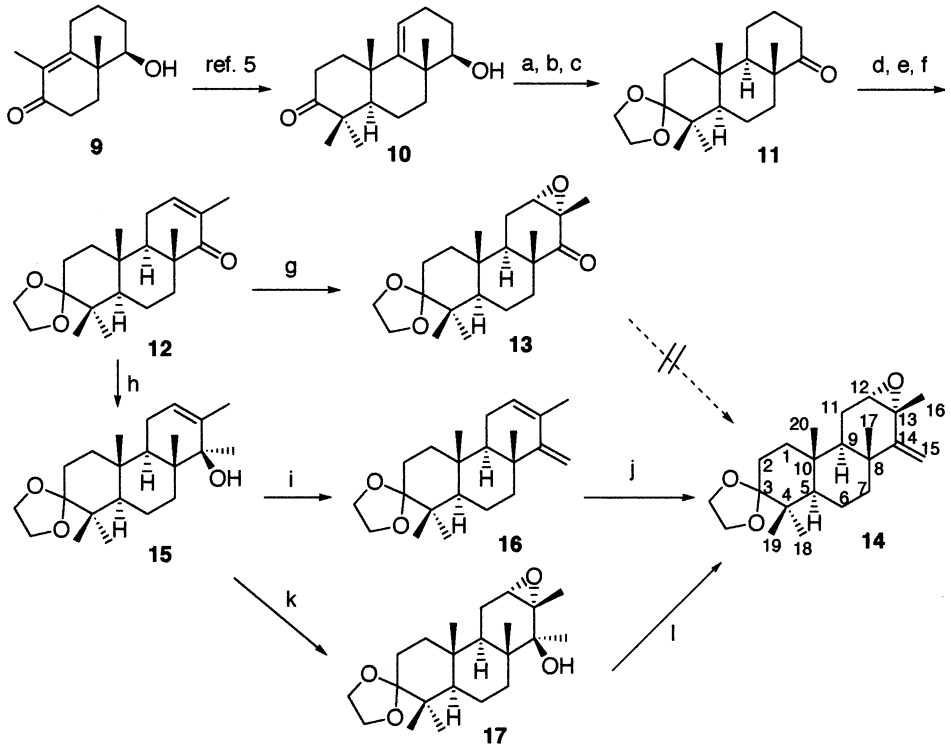


Scheme 1. Synthesis of **6** and synthetic plan for **2**.



Scheme 2. Synthesis of the key intermediate **14**. *Reagents and conditions*: (a) H_2, Pd–C, EtOH (81%); (b) $HO(CH_2)_2OH$, *p*-TsOH, toluene (89%); (c) PDC, 4 Å MS, CH_2Cl_2 (92%); (d) LDA, THF, HMPA; MeI (quant.); (e) LDA, THF, HMPA; PhSeBr; (f) aq. H_2O_2, CH_2Cl_2 (62% in two steps); (g) *t*-BuOOH, triton B, THF (82%); (h) MeLi, THF (quant.); (i) Burgess reagent, toluene (75%); (j) NBS, aq. acetone; NaH, THF (~20%); (k) *m*-CPBA, $NaHCO_3$, CH_2Cl_2 (85%); (l) SO_2Cl_2, pyridine (71%).

ated products as a diastereomeric mixture (quant., α:β = ca. 5:1 based on ^1H NMR analysis). The resulting diastereomeric mixture was treated with LDA and PhSeBr to furnish the corresponding selenide, which was immediately oxidized with H_2O_2 to give enone **12** (62%, two steps).

The next stage was conversion of enone **12** into the key intermediate (**14**). However, this conversion was problematic. Our first attempted route was the sequence **12**→**13**→**14**. Although the diastereoselective epoxidation of **12** was easily achieved by the conventional procedure[7] to furnish α-epoxide **13**, the next methylena-

tion of the carbonyl group was unsuccessful. Thus, an alternative route (**12**→**15**→**16**→**14**) was then examined. Although the first two steps, methylation and dehydration with Burgess reagent,[8] were successful,[9] conversion of the diene **16** into the vinylepoxide **14** was troublesome. We found that Delmond's procedure,[10] which was applied to the preparation of the model vinylepoxide (**7**), gave the desired **14**,[11] but this protocol suffered from low yield and lack of reproducibility.[12] Therefore, we then turned to a third route (**12**→**15**→**17**→**14**). To our delight, it overcame the difficulties as follows. The allylic alcohol **15** was epoxidized with *m*-CPBA to give **17**[13] (85%), which was subsequently dehydrated by treatment with $SOCl_2$ in pyridine to furnish the desired vinylepoxide **14** (71%).

With the key intermediate **14** in hand, the next stage was the crucial step, the coupling of **14** and **8**. As a matter of course, we attempted to adopt our original methodology, palladium-mediated tandem reaction. First, the most promising conditions optimized by model studies[3] were examined (entry 1, Table 1). Surprisingly and unfortunately, the desired spiro-fused adduct **18** and/or **18′** could not be obtained at all. The major by-product was enone **19** probably derived from β-hydride elimination of the π-allylpalladium complex. Thus, we had to review the conditions of the palladium-mediated reaction. In spite of all our efforts, however, no appropriate conditions could be found (entries 2∼5). The reason for these failures might be steric hindrance, because **14** was estimated to be more sterically hindered than the model substrate (**7**) (Scheme 3).

Table 1. Palladium-mediated coupling of **14** and **8**

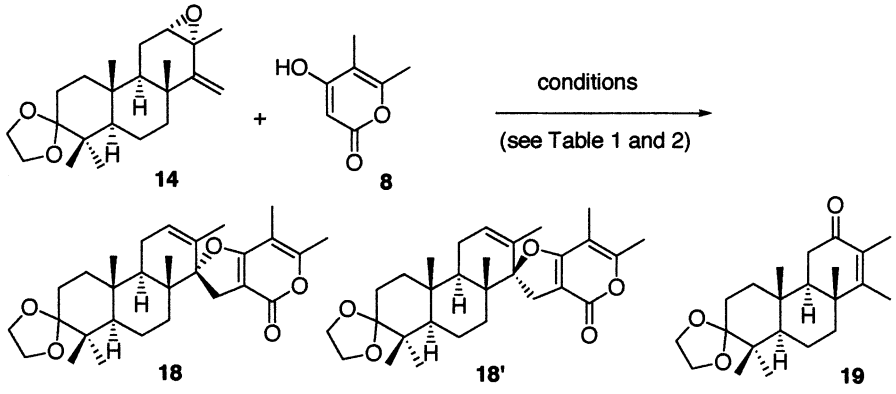
Entry	Catalyst	Base	Conditions	**18** (+**18′**)
1	$Pd(PPh_3)_4$ (7 mol%)	–	Toluene, 100°C, 10 h	–[a]
2	$Pd(PPh_3)_4$ (100 mol%)	–	Toluene, 110°C, 5 h	–[a]
3	$Pd(PPh_3)_4$ (7 mol%)	DBU	Toluene, 110°C, 8 h	NR
4	$Pd(PPh_3)_4$ (7 mol%)	NaH	THF, reflux, 7 h	–[a]
5	$Pd(PPh_3)_4$ (7 mol%)	NaH	Toluene, 110°C, 10 h	Trace[b]

[a] The major product was the enone **19**.
[b] A large part of the starting material **14** was recovered.

Although the above-mentioned unexpected failures were disappointing, the fact that a trace amount of **18** was yielded under the conditions of entry 5 (in the presence of NaH) gave us one hint towards solving the problem. It suggested that **18** might be produced by a simple base-mediated S_N2'-type epoxide-opening and following dehydrative *O*-alkylation, not by a palladium-catalyzed reaction. This speculation prompted us to examine reaction conditions without the palladium catalyst. The representative results are summarized in Table 2. First, addition of a Lewis acid, for enhancing the electrophilicity of vinylepoxide, was attempted. Although these trials were fruitless, we fortunately found that the desired coupling proceeded without any Lewis acid to afforded the mixture of **18** and its epimer **18′** in 29% yield (**18**:**18′** = ca. 6:1 based on ^1H NMR analysis) (entry 3). Thus, we then tried to improve the isolation yield by changing the solvent or the base, but there was no improvement in yield. However, we were eventually able to find that the desired coupling reaction proceeded smoothly without any base (entry 9), furnishing a mixture of **18** and **18′** in 56% yield (**18**:**18′** = ca. 6:1). This result was quite surprising to us, but the α-pyrone **8** might be construed as an activator of the epoxide due to its acidity in this case. In any event, we were able to successfully obtain the desired adduct **18** by the double S_N2'-type tandem reaction.

The chromatographically inseparable mixture of **18** and **18′** was purified by recrystallization (Et_2O) to give the pure **18**. Finally, the protecting group of **18** was removed by treatment with acetic acid to furnish (±)-brevione B (**2**).[14] The overall yield was 10% in 11 steps based on **10** (Scheme 4).

In conclusion, the first synthesis of (±)-brevione B (**2**) was accomplished by employing the double S_N2'-type tandem reaction as a key step. Further optimization of the key step and also enantioselective synthesis of breviones are now in progress in our group.

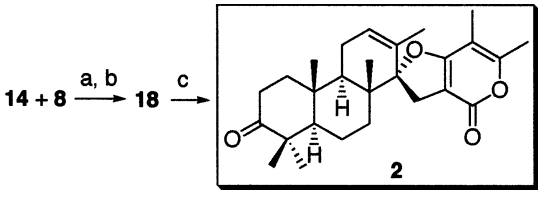


Scheme 3. Synthesis of **18**, the key step.

Table 2. Coupling of **14** and **8** without palladium

Entry	Base	Additive	Conditions	**18**+**18′** (ratio); **14**	**19**
1	NaH	$BF_3{\cdot}OEt_2$	THF, 0°C–rt, 12 h	–[a]	
2	NaH	$Yb(OTf)_3$	THF, 0°C–rt, 12 h	NR	
3	NaH	–	Toluene, 110°C, 24 h	29%[c] (6:1); 28%	40%[c]
4	NaH	HMPA	Toluene, 110°C, 12 h	NR	
5	NaH	–	THF, reflux, 12 h	NR	
6	NaH	–	1,4-Dioxane, reflux, 12 h	NR	
7	*t*-BuOK	–	Toluene, 110°C, 15 h	Trace[b]	Trace
8	Cs_2CO_3	–	Toluene, 110°C, 15 h	<10%[b]	Trace
9	–	–	Toluene, 110°C, 20 h	56%[c] (6:1); 21%	19%[c]
10	–	–	1,4-Dioxane, reflux, 12 h	NR	

[a] The major product was **19**, but it was not isolated.
[b] A large part of the starting material **14** was recovered.
[c] Based on the consumed **14**



Scheme 4. Synthesis of (±)-**2**. *Reagents and conditions*: (a) **8** (2.0 equiv.), toluene, 110°C, 20 h (56% for the mixture of **18** and **18′**); (b) recrystallization from Et_2O (74%); (c) aq. AcOH, 40°C (quant.).

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9. The direct methylenation of **12** to **16** was not successful by usual procedures such as the Wittig reaction, Peterson reaction and Tebbe reagent.
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11. The α-orientation of the oxirane-ring could not be confirmed by NOE studies. However, it is clearly supported by the fact that 12-H is observed as a triplet ($J=1.8$ Hz), because the results of MM2 and MOPAC calculations suggest that dihedral angles between 11-H_2 and12-H are both ca. 60° in **14**, while they should be 90° and 30° in its β-isomer. The numbering in this paper corresponds to that of breviones reported in Ref. 2.
12. It was noted that conventional epoxidation with *m*-CPBA, dimethyldioxirane, etc., did not work.
13. The α-orientation of the oxirane-ring was not certain at this stage, but it was confirmed by its conversion into **14**. The reason for the selectivity might be steric hindrance due to the angular methyl group.
14. Properties of (±)-**2**: colorless micro crystals; mp 186–188°C (from hexane–EtOAc); IR ν_{max} (CCl_4) 1725 (s, C=O), 1710 (m, C=O) 1655 (w, C=C) cm^{-1}; EIMS *m*/*z* (rel. int.) 424 (100), 409 (17), 382 (6), 352 (13), 271 (15), 218 (20), 179 (23), 154 (76), 119 (40); HREIMS obsd 424.2605 calcd for $C_{27}H_{36}O_4$ 424.2614; ^1H NMR (300 MHz, $CDCl_3$) $\delta=0.96$ (3H, s), 1.06 (3H, s), 1.09 (6H, s), 1.34 (2H, m), 1.45–1.62 (4H, m), 1.65 (3H, br d, $J=1.2$ Hz), 1.75 (1H, t-like, $J=8.4$ Hz), 1.93 (3H, s), 1.95 (1H, m), 2.05 (2H, m), 2.22 (3H, s), 2.41 (1H, ddd, $J=15.8$, 6.8, 3.9 Hz), 2.58 (1H, ddd, $J=15.8$, 11.1, 7.2 Hz), 2.90 (1H, d, $J=15.7$), 3.05 (1H, d, $J=15.7$), 5.67 (1H, br s); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=9.7$, 15.5, 16.0, 17.2, 18.4, 19.0, 21.5, 23.2, 26.4, 28.7, 31.8, 34.0, 36.5, 38.9, 40.9, 47.0, 47.4, 55.1, 99.5, 99.6, 102.8, 127.8, 131.8, 160.4, 162.0, 171.1, 217.2.