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Synthetic studies on breviones: construction of the CDE ring system

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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 synthesis of a structurally simplified model compound (**8**), corresponding to the characteristic spiro-fused CDE ring portion of **1**–**4**, was accomplished by employing sequential, double nucleophilic substitution reactions as the key steps. © 2002 Published by Elsevier Science Ltd.

In 2000, Macías et al. isolated breviones A–E (**1**–**5**) from *Penicillium brevicompactum* Dierckx as allelopathic agents.[1] 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, and only two similar skeletons have been reported in the cases of lygodinolide (**6**, antifertility agent isolated from *Lygodium flexuosum*)[2,3] and stypoldione (**7**, ichthyotoxic agent against *Eupomacentrus leucosticus* isolated from *Stypopodium zonale*).[4,5] We became interested in the structure of breviones from a synthetic point of view and initiated our synthetic studies on them. Because a crucial point in the synthesis of breviones should be the construction of the characteristic spiro-fused CDE ring framework, a model compound (**8**) was assigned as the prime target. Herein, we report the synthesis of **8** as a part of our synthetic studies (Fig. 1).

As shown in Scheme 1, our strategy for the synthesis of **8** was based on double nucleophilic substitution reactions, by which direct conversion of **9** and **10** to **8** would be possible. For the first *C*-alkylation reaction (**9**+**10**→**11**), palladium(0)-mediated nucleophilic substitution reaction via a π-allylpalladium complex was thought to be appropriate.[6,7] For the second intramolecular cyclization (**11**→**8**), we envisaged adopt-

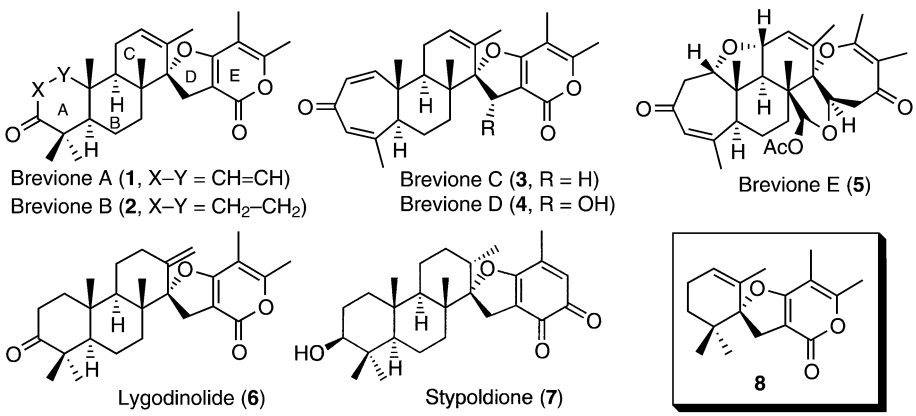

Figure 1. Structures of breviones and other related natural products.

Keywords: diterpenoids; allelopathic agents; tandem reaction; palladium catalyst.
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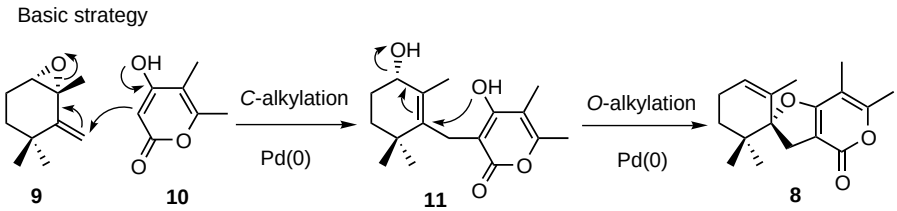
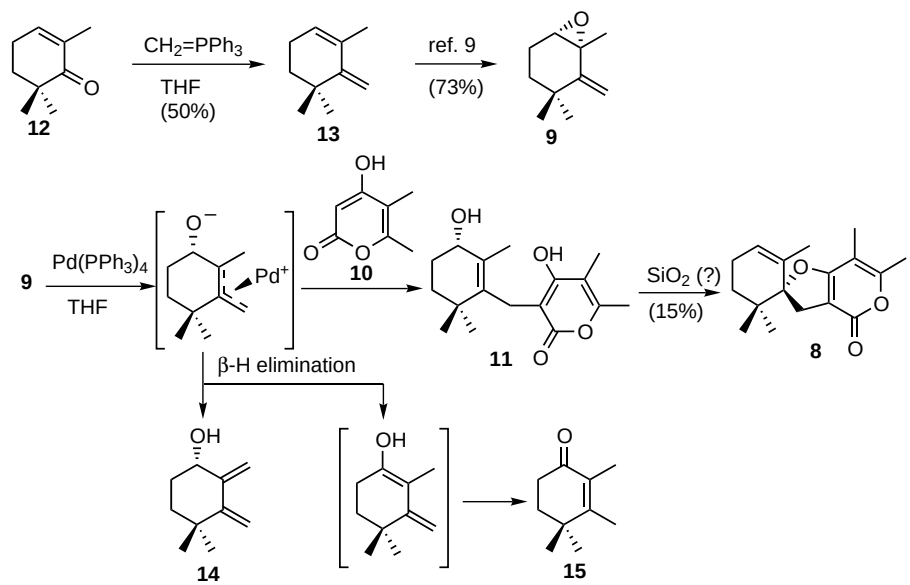


Scheme 1. Synthetic plan for **8**.

ing palladium-catalyzed dehydrative *O*-alkylation. If both of these two alkylations take place in one-pot, the tandem reaction should be ideally accomplished. However, we anticipated that the second *O*-alkylation might be difficult to achieve, since an allylic alcohol is known to be less reactive for the formation of π-allylpalladium complex than the corresponding acetate or some other derivatives.[6,8] Actually, no application of a vinyl epoxide to palladium-mediated tandem reaction has been so far reported.

Our synthetic route to **8** is illustrated in Scheme 2. First, we synthesized the known vinyl epoxide **9**[9] from enone **12**[10] via diene **13**.[11] The α-pyrone **10** was also prepared according to the reported procedure.[12] These two substrates were employed for the next key step. As an initial attempt, a mixture of **9** and **10** was treated with $Pd(PPh_3)_4$ (7 mol%) in refluxing THF. As one of the substrates, **9**, was smoothly consumed, three new products appeared on TLC. One of them was suggested to be **11** judging from the behavior on TLC. It was likely that the first *C*-alkylation took place but the second *O*-alkylation did not occur. Unfortunately, attempted isolation of **11**[13] failed because of the unexpected degradation of **11** during the course of SiO_2 chromatography. However, we became aware of the appearance of *a new product* to be isolated in 15% yield. Surprisingly and fortunately, *the new product* proved to be the target compound **8** based on various spectral analyses.[14] On the other hand, the two other products were elucidated to be **14**[9] and **15**,[9] respectively, which might be derived from β-hydride elimination of the π-allylpalladium complex.[15]

We then began the optimization of reaction conditions as shown in Table 1. Our first subject was to clarify what could convert **11** to **8**. The effect of an acid was examined, because SiO_2 was thought to be an acidic promoter of this intramolecular *O*-alkylation. After the coupling of **9** and **10**, *p*-TsOH (catalytic amount) was added to the reaction mixture. Predictably, the formation of **8** was observed along with the consumption of **11**, and **8** was obtained in 25% yield after chromatographic purification (entry 1). Now it was clear that this *O*-alkylation could be catalyzed by an acid.[16] Encouraged by this result, we tried to improve the isolation yield. By the screening of solvents (entries 2–4), toluene was found to be the best, providing better yield (36%). It was noteworthy that the yielded product was not **11** but **8** in toluene even before treatment with *p*-TsOH. The mechanism of the dehydrative *O*-alkylation is uncertain, but at any rate the desired tandem reaction took place in toluene indeed.[17]

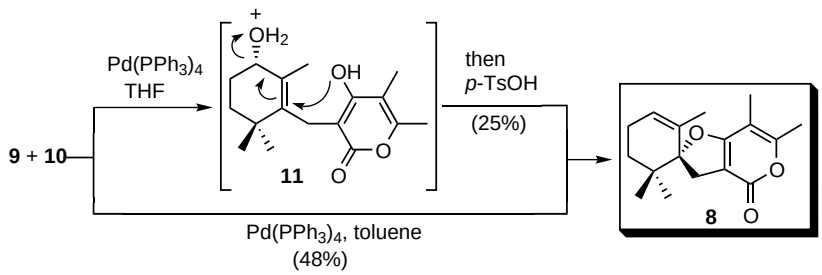


Scheme 2. Synthesis of **8** (1).

Table 1. Palladium-mediated coupling of **9** and **10** to **8**

Entry	Catalyst	Conditions[a]	**8** (%)	**14**, **15** (%)
1	$Pd(PPh_3)_4$	THF, reflux, 6 h; then *p*-TsOH[b]	25	10, 39
2	$Pd(PPh_3)_4$	Toluene, 70°C, 6 h	36	5, 31
3	$Pd(PPh_3)_4$	DMF, 70°C, 5 h; then *p*-TsOH[b]	Trace	–[c]
4	$Pd(PPh_3)_4$	CH_2Cl_2, reflux, 50 h; then *p*-TsOH[b]	25	13, 40
5	$Pd(PPh_3)_4$	Toluene, 100°C, 3 h	48	6, 30
6	$Pd(PPh_3)_4$ (30 mol%)	Toluene, 100°C, 3 h	Decomp.	–
7	$Pd(PPh_3)_4$	Toluene (0.4 ml), 100°C, 3 h	Decomp.	–
8	$Pd(PPh_3)_4$	Et_3N (1.1 equiv.), toluene, 100°C, 6 h	20	–[c]
9	$Pd(PPh_3)_4$	DBU (1.1 equiv.), toluene, 100°C, 6 h	25	–[c]
10	$Pd(dba)_2$	Toluene, 100°C, 5 h	28	4, 41
11	$Pd(dppe)_2$[d]	Toluene, 100°C, 25 h	35	4, 34
12	$Pd(dppp)_2$[d]	Toluene, 100°C, 15 h	25	–[c]
13	$Pd(dppb)_2$[d]	Toluene, 100°C, 5 h	Trace	–[c]
14	$Pd(dppf)_2$[d]	Toluene, 100°C, 6 h	Trace	–[c]
15	$Pd(PBu_3)_4$[d]	Toluene, 100°C, 5 h	15	–[c]
15	$Pd[P(O\text{-}^iPr)_3]_4$[d]	Toluene, 100°C, 3 h	36	–[c]

[a] General procedure: The mixture of **9** (20.0 mg, 131 μmol) and **10** (19.0 mg, 135 μmol) in solvent (1 ml) was treated with catalyst (7 mol%) under the given conditions unless otherwise stated.
[b] *p*-TsOH (0.1 equiv.) was added to the reaction mixture, and the stirring was continued for 1 h at rt.
[c] As with other entries, **14** and **15** were yielded, but were not isolated.
[d] The catalyst was prepared in situ by mixing $Pd(dba)_2$ with a ligand in an appropriate ratio.



Scheme 3. Synthesis of **8** (2).

Since the isolation yield was still unsatisfactory, we tried to tune some reaction conditions (entries 5–7). When the reaction was performed at higher temperature, better yield (48%) was observed, while only inferior results were obtained with more catalyst (30 mol%) or in higher concentration (×2.5). The addition of a base, for enhancing the nucleophilicity of **10**, was then examined (entries 8 and 9), but it gave no remarkable improvement in yield. However, interestingly, **8** was also obtained even in the presence of a base, suggesting that this *O*-alkylation was catalyzed by palladium, not by the acidity of pyrones **10** and/or **11**. Although the accurate reaction mechanism is still uncertain, the *O*-alkylation may proceed via a π-allylpalladium complex in toluene.[16] Other ligands on palladium(0) were also examined instead of PPh_3 (entries 10–15), but there was no improvement in yield. As a result, the condition listed in entry 5 turned out to be the best for the desired tandem reaction (Scheme 3).

In conclusion, the synthesis of **8**, the CDE ring model compound of breviones A–D (**1**–**4**), was accomplished by direct coupling of **9** and **10**. The key reactions were palladium(0)- mediated *C*-alkylation of vinyl epoxide **9** and subsequent dehydrative *O*-alkylation. To the best of our knowledge, this must be the first example of a vinyl epoxide undergoing palladium-mediated sequential, double nucleophilic substitution reactions in one-pot.[18] For the dehydrative *O*-alkylation, we also found that it was catalyzed by an acid. The developed simple and efficient tandem reaction process will make the convergent synthesis of breviones possible. In our group, further optimization of this key process directed toward the total synthesis of breviones A (**1**) and B (**2**) is now in progress.

Acknowledgements

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References

1. (a) Macías, F. A.; Verela, R. M.; Simonet, A. M.; Cutlar, H. G.; Cutlar, S. J.; Dugan, F. M.; Hill, R. A. *J. Org.*

Chem. **2000**, *65*, 9039; (b) Macías, F. A.; Verela, R. M.; Simonet, A. M.; Cutlar, H. G.; Cutlar, S. J.; Ross, S. A.; Dunbar, D. C.; Dugan, F. M.; Hill, R. A. *Tetrahedron Lett*. **2000**, *41*, 2683.

2. Isolation: Achari, B.; Chaudhuri, C.; Saha, C. R.; Pakrashi, S. C. *J. Org. Chem*. **1990**, *55*, 4977.
3. Synthetic study: Banerjee, A. K.; Achari, B. *Tetrahedron Lett*. **1993**, *34*, 1209.
4. Isolation: Gerwick, W. H.; Fenical, W.; Fritsch, N.; Clardy, J. *Tetrahedron Lett*. **1979**, *20*, 145.
5. Synthesis: (a) Mori, K.; Koga, Y. *Bioorg. Med. Chem. Lett*. **1992**, *2*, 391; (b) Mori, K.; Koga, Y.; *Liebigs Ann*. **1995**, 1755.
6. (a) Tsuji, J. *Palladium Reagents and Catalyst*, *Innovations in Organic Synthesis*; John Wiley & Sons: Chichester, 1995; pp. 250–422; (b) Trost, B. M.; Verhoeven, T. R. In *Comprehensive Organometallic Chemistry*; Wilkinson, G.; Stone, F. G. A.; Abel, E. W., Eds.; Pergamon Press: Oxford, 1982; Vol. 8, pp. 799–853.
7. (a) Tsuji, J.; Kataoka, H.; Kobayashi, Y. *Tetrahedron Lett*. **1981**, *22*, 2575; (b) Trost, B. M.; Molander, G. A. *J. Am. Chem. Soc*. **1981**, *103*, 5969; (c) Mereno-Mañas, M.; Prat, M.; Ribas, J.; Virgili, A. *Tetrahedron Lett*. **1988**, *29*, 581.
8. (a) Bergbreiter, D. E.; Weatherford, D. A. *J. Chem. Soc., Chem. Commun*. **1989**, 883; (b) Tenaglia, A.; Kammerer, F. *Synlett* **1996**, 576; (c) Kimura, M.; Horino, Y.; Mukai, R.; Tanaka, S.; Tamaru, Y. *J. Am. Chem. Soc*. **2001**, *123*, 10401 and references cited therein.
9. Boulin, B.; Miguel, B. A.-S.; Delmond, B. *Tetrahedron* **1998**, *54*, 2753.
10. Horii, Z.-I.; Yagami, T.; Ito, M.; Hanaoka, M. *Chem. Pharm. Bull*. **1968**, *16*, 848.
11. Kane, B. J.; Von Genk, R. A.; US patent, US-4179468 (1979) and 4244890 (1980).
12. (a) Harris, T. M.; Harris, C. M.; Wachter, M. P. *Tetrahedron* **1968**, *24*, 6897; (b) Bonsignore, L.; Cabiddu, S.; Loy, G.; Secci, D. *Heterocycles* **1989**, *29*, 913; (c) Hagiwara, H.; Fujimoto, N.; Suzuki, T.; Ando, M. *Heterocycles* **2000**, *53*, 549.
13. Because of the scarcity and the low purity, clear spectral data of **11** could not be obtained. However, the following ^{1}H NMR data, which could be picked up, suggested that the structure of **11** must be correct tentatively. ^{1}H NMR (250 MHz, $CDCl_3$) $\delta=1.04$ (3H, s), 1.05 (3H, s), 1.79 (6H, s), 2.19 (3H, s), 3.29 (2H, s), 4.03 (1H, br t, $J=4.1$).
14. Properties of **8**: pale yellow needles; mp 99–100°C (from hexane); IR ν_{max} (CCl_4) 1720 (s, C=O), 1650 (w), 1580 (m), 1270 (m), 1115 (w), 1050 (w), 930 (w), 870 (w) cm^{-1}; EIMS m/z (rel. int.) 274 (100), 259 (24), 232 (20), 218 (32), 202 (31); HREIMS obsd 274.1571 calcd for $C_{17}H_{22}O_3$ 274.1568; ^{1}H NMR (300 MHz, $CDCl_3$) $\delta=0.90$ (3H, s), 1.02 (3H, s), 1.54 (2H, m), 1.63 (3H, br s), 1.93 (3H, s), 2.05 (2H, m), 2.22 (3H, s), 2.84 (1H, d, $J=15.6$), 3.11 (1H, d, $J=15.6$), 5.46 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta=9.2$, 16.9, 17.4, 22.0, 22.3, 22.5, 32.6 (two peaks), 36.9, 98.3, 99.3, 102.8, 124.4, 134.6, 160.1, 161.7, 171.6.
15. Suzuki, M.; Noyori, R. *J. Am. Chem. Soc*. **1979**, *101*, 1623.
16. There was no information concerning the relative stereochemistry between the hydroxy group of **11** and the newly formed C–O bond of **8**, because all of our products were racemates.
17. Bergbreiter and his co-worker have reported $Pd(PPh_3)_4$-catalyzed allylation of acetoacetates with allyl alcohols in toluene.[8a]
18. Although some groups have already reported palladium-mediated double nucleophilic substitutions of a vinyl epoxide, these are achieved in a stepwise manner. Boeckman, R. K., Jr.; Shair, M. D.; Vargas, J. R.; Stolz, L. A. *J. Org. Chem*. **1993**, *58*, 1295 and Ref. 8b.