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First synthesis and absolute configuration of decaturin D

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Abstract—The first synthesis of (+)-decaturin D (**1**), an antiinsectant diterpenoid isolated from *Penicillium thiersii*, was accomplished by employing our original spiro-cyclization reaction as the key step. The absolute configuration of the naturally occurring **1** was determined.

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Decaturin D (**1**) was isolated from the extracts of *Penicillium thiersii* by Gloer and his co-workers as an antiinsectant agent.[1] Some other relatives, decaturins A–C (**2**–**4**), oxalicines A and B (**5** and **6**), 15-deoxyoxalicines A and B (**7** and **8**), have also been isolated from *P. thiersii* and/or *Penicillium decaturense*.[1–3] These compounds are structurally unique natural products consisting of diterpene, polyketide, and nicotinate subunits. Especially, the spiro-linkage between diterpene and polyketide subunits is characteristic and noteworthy. On the other hand, there are some closely related diterpenoid derivatives which are breviones isolated from *Penicillium* sp. as allelochemicals.[4] In particular, the structure of decaturin D (**1**) is exactly similar to that of brevione B (**9**), except for the substituents on the α-pyrone ring as shown in Figure 1. Additionally, the α-pyrone ring with the 3-pyridyl group of decaturins[5] is identical to that of pyripyropenes, potent acyl-CoA cholesterol acyltransferase (ACAT) inhibitors isolated from *Aspergillus fumigatus*.[6] The structure of pyripyropene A (**10**) is shown in Figure 1. The above-mentioned structural similarities between decaturins, breviones, and pyripyropenes suggest that decaturins may exhibit some valuable bioactivities other than antiinsectant activity and the potential as a new 'lead' for agrochemicals and/or pharmaceuticals.

Since we have been engaged in synthetic studies on breviones,[7,8] we became interested in synthesizing decaturins and initiated our studies toward their synthesis in the course of nature. First, we decided to begin with the synthesis of decaturin D (**1**), whose structure is the simplest among decaturins and is quite similar to that of **9**, as mentioned above. Thus, not only the basic strategy but also the key intermediate of our synthesis of **9** must be applicable for the enantiospecific synthesis of **1**. Herein we report the first synthesis of (+)-**1** and determination of the absolute configuration of the naturally occurring **1**.

Our synthetic plan was completely based on that for brevione B (**9**), as shown in Scheme 1. Because the only structural difference between **1** and **9** is the substituent on the α-pyrone ring, the key intermediate (−)-**12**[8b] for the synthesis of (+)-**9** could be diverted. Thus, the success of this synthesis depended entirely upon whether the key spiro-cyclization would proceed with α-pyrone **11**[9] or not. However, there was fear that the pyridine moiety of **11** might have a negative effect on this crucial step, because it was speculated that the weak acidity of γ-hydroxy-α-pyrone was important to activate a vinylepoxide. In this case, the pyridine basicity might counteract the acidity. Indeed, our original spiro-cyclization did not proceed smoothly in the presence of a base.[8] Therefore, we first undertook model studies to assess the process.

Vinylepoxide (±)-**18** was assigned as a model substrate. This was easily prepared from Wieland–Miescher ketone (±)-**15** via the known ketone **16**[10] as follows. Methylation of **16** was followed by unsaturation to give **17**. Enone **17** was then converted to the model compound (±)-**18** by the following three steps: (i) treatment with MeLi (93%); (ii) epoxidation with *m*-CPBA (98%)

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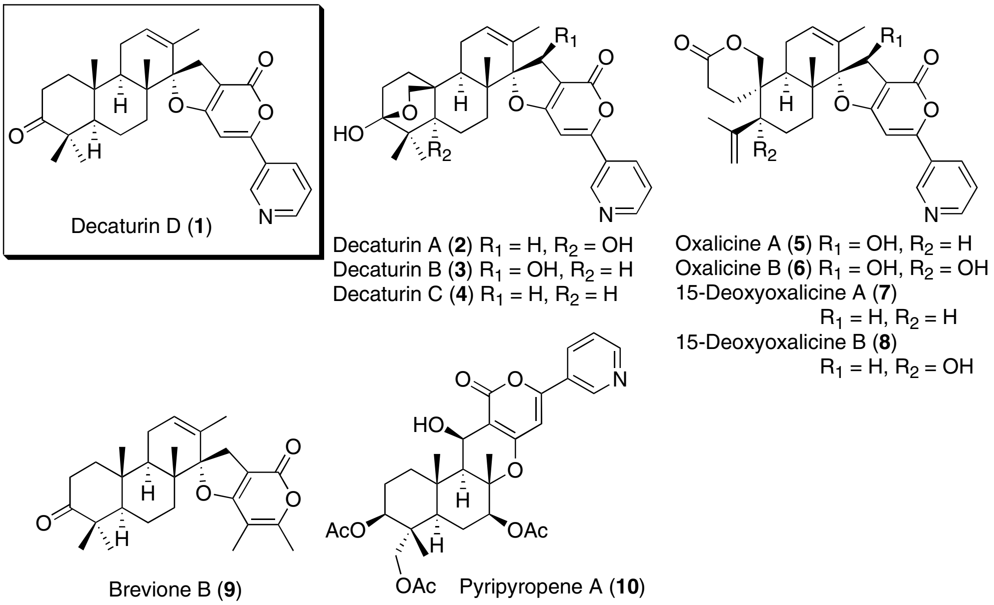
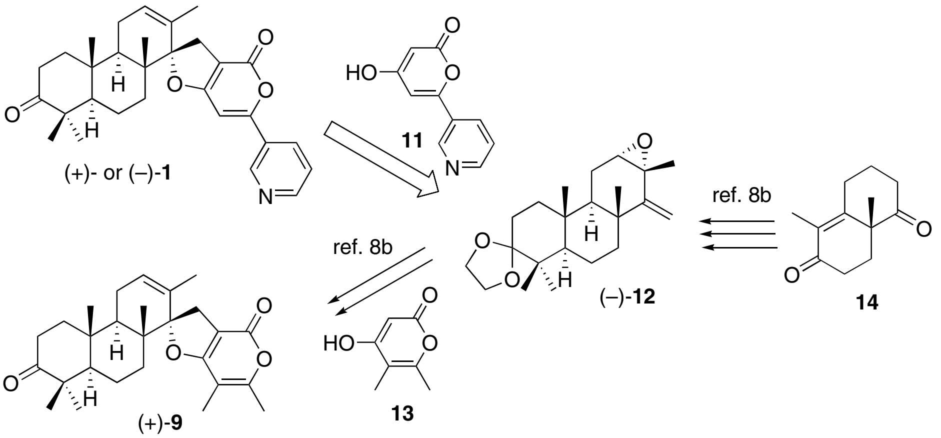


Figure 1. Structures of decaturins.



Scheme 1. Synthetic plan for decaturin D (**1**).

and (iii) dehydration (90%). This process was analogous to our brevione synthesis. With the model substrate (±)-**18** in hand, we examined the key spiro-cyclization with α-pyrone **11**,[9] as shown in Table 1. Unfortunately, our premonition proved right, which means that the desired spiro-adducts (**19**/**19′**) was obtained in only 13% yield by heating (±)-**18** and **11** in toluene under reflux for 36 h (entry 1). The isolated yield was considerably low in comparison with the case of brevione synthesis. At that time the desired spiro-adducts were isolated in 44% yield,[8] even though the reaction conditions were almost identical. The probable reasons for the low yield might be the above-mentioned negative effect of the pyridine basicity and the low solubility of **11**. In fact, pyrone **11** was poorly soluble in refluxing toluene. Although the former problem was not so easy to deal with, the latter was thought to be solved rather easily by selecting appropriate conditions, for example, using a more polar and/or higher boiling point solvent. However, optimization of the solvent was not straightforward, because we have already known that our original spiro-cyclization preferred non-polar aromatic solvents to polar solvents.[8] Thus, we carefully examined several solvents on the coupling of (±)-**18** with **11**. The isolated yield was slightly improved by using xylene or chlorobenzene (entries 2 and 3), but the relatively polar solvents, except for anisole, diminished the yield (entries 4–7). This tendency was in accord with our already acquired knowledge. The epimeric ratio of **19**/**19′** was 12:1 or better in all cases. It was also noted that the major by-products were enone **20** and alcohol **21**, as in the case of our former studies. Although the isolated yields were still far from satisfactory, xylene, and anisole were assigned as hopeful candidates. The reaction rate of chlorobenzene was considerably inferior (Scheme 2).

We then executed the spiro-cyclization of (−)-**12** with **11** in xylene or anisole. As a result, anisole was found to be the better solvent,[11] affording the desired adduct (+)-**22**/**22′** in 51% yield (65% based on the recovered SM). The

Table 1. Studies on the key spiro-cyclization

Entry	Substrate	Solvent	Temperature (°C); time (h)	Products (ratio)[a]	Yield[b] (%)
1	(±)-**18**	Toluene	110; 36	**19**/**19′** (>20:1)	13[c]
2	(±)-**18**	*o*-Xylene	145; 8	**19**/**19′** (25:1)	21 (26)[d]
3	(±)-**18**	Chlorobenzene	132; 18	**19**/**19′** (20:1)	22[c]
4	(±)-**18**	Diphenyl ether	150;[e] 17	**19**/**19′** (12:1)	11[c]
5	(±)-**18**	Pyridine	115; 24	**19**/**19′** (−)	Trace[c]
6	(±)-**18**	Nitrobenzene	150;[e] 20	**19**/**19′** (12:1)	5[c]
7	(±)-**18**	Anisole	154; 4	**19**/**19′** (17:1)	28 (31)[d]
8	(−)-**12**	Xylene	145; 7	(+)-**22**/**22′** (⩾40:1)	33 (43)[d]
9	(−)-**12**	Anisole	154; 6	(+)-**22**/**22′** (⩾40:1)	51 (65)[d]

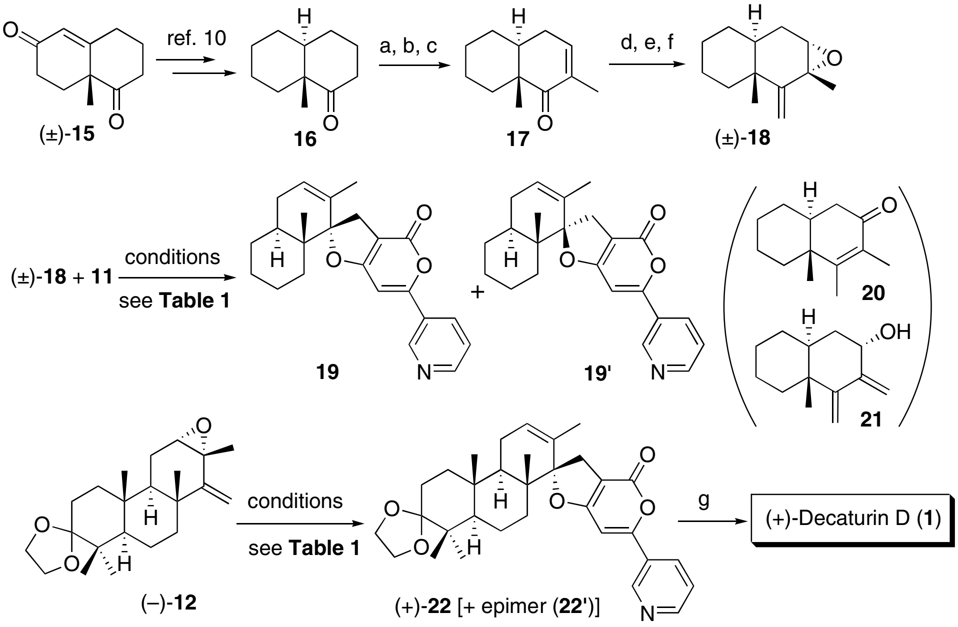
[a] Based on ^{1}H NMR analysis.

[b] Isolated yield.

[c] A certain amount of the starting material was recovered.

[d] Based on the recovered SM.

[e] Bath temperature.



Scheme 2. Synthesis of the model compound **19** and (+)-decaturin D (**1**). Reagents and conditions: (a) LDA, THF; MeI (94%); (b) (i) Ac_2O, cat. $HClO_4$, CCl_4; (ii) NBS, aq THF; (c) Li_2CO_3, DMF (71% in 2 steps); (d) MeLi, THF (93%); (e) *m*-CBPA, $NaHCO_3$, CH_2Cl_2 (98%); (f) $SOCl_2$, pyridine (90%); (g) aq AcOH; recrystallization (60%).

ratios of (+)-**22**/**22′** were both ⩾40:1 in entries 8 and 9. Although it was not ascertained why better yield was observed in comparison with the model case, it might be due to the better stability of (−)-**12**. The degradation of (±)-**18** to **20** and **21** was certainly faster than that of (−)-**12** to the corresponding enone and alcohol under the same conditions. In any event, we were able to obtain the desired adducts (+)-**22**/**22′** in moderate but acceptable yield by our original method. The yielded (+)-**22**/**22′** was deprotected by treatment with aq AcOH to give the crude (+)-**1**, which was then purified to give the pure (+)-decaturin D (**1**) (60% after recrystallization), $[\alpha]_D^{27}$ +140 (*c* 0.12 in CH_2Cl_2), {lit.,[1] $[\alpha]_D$ +58 (*c* 0.1 in CH_2Cl_2)}. The various spectral data of synthetic (+)-**1** were in good accord with those of the natural product.[12] It was also noteworthy that the synthesized (+)-**1** was a crystal, mp 141–144 °C (from hexane–Et_2O), while the reported natural decaturin D was an oil.[1] The absolute configuration of naturally occurring decaturin D (**1**) was therefore determined as shown in Figure 1.

In conclusion, we were able to accomplish the first synthesis of (+)-decaturin D (**1**) by employing our original spiro-cyclization as the key step. We were also able to determine the absolute configuration of naturally occurring decaturin D. Furthermore, it can be easily deduced that other decaturins must have the same absolute configuration. Further studies toward the total synthesis of other decaturins are now in progress in our group.

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11. The advantage of anisole as a solvent for our spirocyclization was also demonstrated by our synthesis of brevione B.[8b]
12. Properties of synthetic (+)-**1**: colorless needles (from hexane–Et_2O); mp = 141–144 °C; $[\alpha]_D^{27}$ +140 (*c* 0.12, CH_2Cl_2); IR ν_{max} (CH_2Cl_2) 1720 (s, C=O), 1630 (w, C=C) cm^{-1}; HREIMS (M^+) obsd 473.2558 calcd for $C_{30}H_{35}O_4N_1$ 473.2566; ^1H NMR (300 MHz, $CDCl_3$) $\delta = 0.99$ (3H, s), 1.07 (3H, s), 1.09 (6H, s), 1.38–1.68 (6H, m), 1.70 (3H, br d, $J = 1.5$ Hz), 1.78 (1H, dd, $J = 9.3$, 7.5 Hz), 1.95 (1H, ddd, $J = 13.2$, 7.2, 3.9 Hz), 2.09 (2H, m), 2.43 (1H, ddd, $J = 15.9$, 7.2, 3.9 Hz), 2.57 (1H, ddd, $J = 15.9$, 10.5, 7.2 Hz), 2.97 (1H, d, $J = 16.5$ Hz), 3.12 (1H, d, $J = 16.5$ Hz), 5.73 (1H, br s), 6.65 (1H, s), 7.39 (1H, br dd, $J = 8.1$, 4.8 Hz), 8.14 (1H, ddd, $J = 8.1$, 2.4, 1.8 Hz), 8.68 (1H, dd, $J = 4.8$, 1.8 Hz), 9.03 (1H, br d, $J = 2.4$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 15.5$, 16.0, 18.5, 19.0, 21.4, 23.2, 26.5, 28.3, 31.7, 34.0, 36.5, 38.7, 40.9, 46.9, 47.3, 54.5, 93.8, 100.8, 102.0, 123.6, 127.6, 128.4, 131.4, 133.2, 147.0, 151.5, 160.2, 160.8, 170.1, 217.1.