

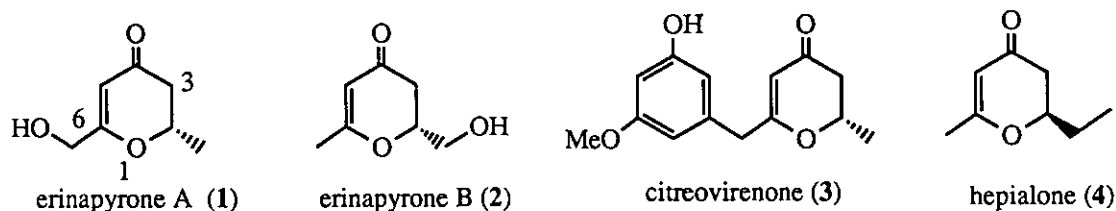
## ASYMMETRIC SYNTHESSES OF (-)-ERINAPYRONES A AND B

Yoshihiro Noda,\* Takeshi Fukaya, and <sup>The late</sup>Mitsuko Kikuchi

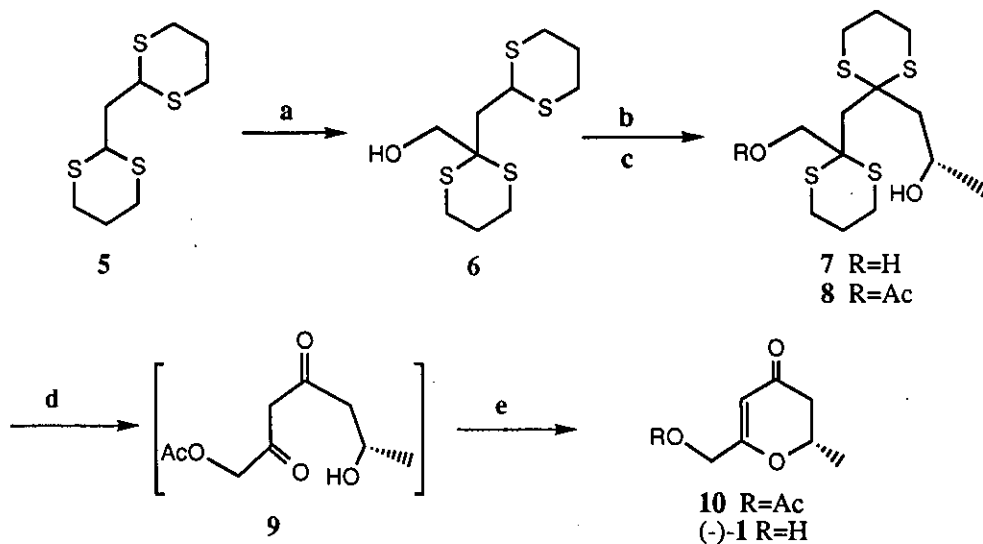
Department of Industrial Chemistry, College of Engineering, Nihon University  
Tamura-machi, Koriyama, Fukushima 963, Japan

**Abstracts---** (-)-Erinapyrone A and (-)-erinapyrone B have been synthesized in short steps from *bis*-2-(1,3-dithianyl)methane, (*S*)-propylene oxide and (*R*)-benzyl glycidyl ether. These synthetic compounds, however, showed higher specific rotation values than those of the natural products. Both enantiomers of erinapyrones A and B were synthesized by the use of antipodal epoxides. These enantiomers showed same specific rotation values with reverse signs. The racemic compounds were also synthesized as standard samples for analysis on chiral gc column for optical resolution.

Erinapyrone A (**1**) and erinapyrone B (**2**) were isolated from the culture-broth of *Hericium erinaceum* mycelia by Kawagishi *et al.*<sup>1</sup> The structures of **1** and **2** were determined to be (*2S*)-2,3-dihydro-6-hydroxymethyl-2-methyl-4*H*-pyran-4-one and (*2R*)-2,3-dihydro-2-hydroxymethyl-6-methyl-4*H*-pyran-4-one. The absolute configurations **1** and **2** were suggested by comparison of their cd spectra with those of citreovirenone (**3**)<sup>2</sup> and hepialone (**4**),<sup>3</sup> respectively. It has reported that **1** and **2** possess cytotoxicity toward HeLa cells.<sup>1</sup> We become interested in clarifying the absolute stereostructure of **1** and **2**. We now wish to report the first synthesis of optically active (-)-**1** and (-)-**2** in short steps starting from *bis*-2-(1,3-dithianyl)methane (**5**),<sup>5</sup> (*S*)-propylene oxide and (*R*)-benzyl glycidyl ether.

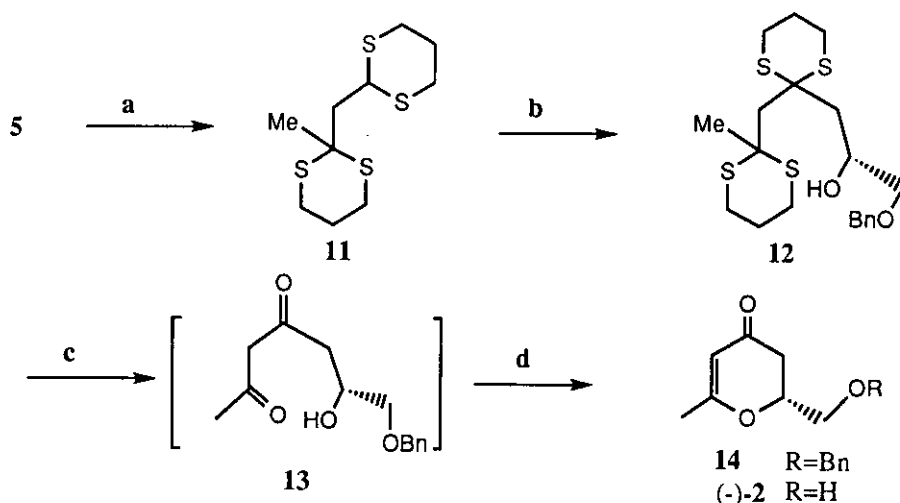


The treatment of **5** with *n*-BuLi in THF at  $-18\text{ }^{\circ}\text{C}$  for 2 h followed by the adding gaseous HCHO afforded monoalcohol (**6**) in 75% yield. Coupling of dianion generated from **6** by treatment with 2 eq. of *n*-BuLi in THF with (*S*)-propylene oxide gave the diol (**7**),  $[\alpha]_{\text{D}}^{27} + 2.53^{\circ}$  (c 1.52  $\text{CHCl}_3$ ), in 60% yield. Acetylation of the primary hydroxyl group of **7** by 1 eq. of acetic anhydride in pyridine yielded the monoacetate (**8**),  $[\alpha]_{\text{D}}^{24} + 1.08^{\circ}$  (c 0.86  $\text{CHCl}_3$ ), in 67% yield. Hydrolysis of 1,3-dithiane parts of **8** with 5 eq. of  $\text{HgCl}_2$  in the presence of  $\text{CaCO}_3$  in aqueous MeCN gave an intermediary diketone (**9**) containing a small amount of  $\gamma$ -pyrone (**10**). If the reaction mixture was stirred without  $\text{CaCO}_3$ , only the  $\gamma$ -pyrone (**10**),  $[\alpha]_{\text{D}}^{18} - 139.8^{\circ}$  (c 0.962  $\text{CHCl}_3$ ) was isolated in 45% yield. Hydrolysis of **10** with  $\text{K}_2\text{CO}_3$  in aqueous MeOH gave the (-)-erinapyrone A ((-)-**1**), mp  $41\text{--}43\text{ }^{\circ}\text{C}$  in 77% yield (Scheme 1).



**Scheme 1.** Reagents and conditions : (a) *n*-BuLi, THF, HCHO gas, 75%; (b) 2 eq. *n*-BuLi, THF (*S*)-propylene oxide; 60%; (c) 1 eq.  $(\text{AcO})_2\text{O}$ , Py; 67%; (d)  $\text{HgCl}_2$ , MeCN,  $\text{H}_2\text{O}$ ; 45%; (e)  $\text{K}_2\text{CO}_3$ , MeOH,  $\text{H}_2\text{O}$ ; 77%.

Alkylation of **5** with methyl iodide, employing 1 eq. of *n*-BuLi, gave the monomethylated compound (**11**) in 96% yield. Coupling of an anion generated from **11** by treatment with 1 eq. of *n*-BuLi with (*R*)-benzyl glycidyl ether gave the alcohol (**12**),  $[\alpha]_D^{20} +1.35^\circ$  (c 4.42 CHCl<sub>3</sub>), in 56% yield. Alcohol (**12**) was directly converted to the corresponding  $\gamma$ -pyrone (**14**),  $[\alpha]_D^{30} -155.8^\circ$  (c 1.46 CHCl<sub>3</sub>), by the treatment with HgCl<sub>2</sub> in aqueous MeCN in 55% yield. Deprotection of benzyl group with BF<sub>3</sub>-Et<sub>2</sub>O and dimethyl sulfide in CH<sub>2</sub>Cl<sub>2</sub> at room temperature<sup>6</sup> gave the (-)-erinapyrone B ((-)-**2**), mp 50-52 °C in 71% yield (Scheme 2).

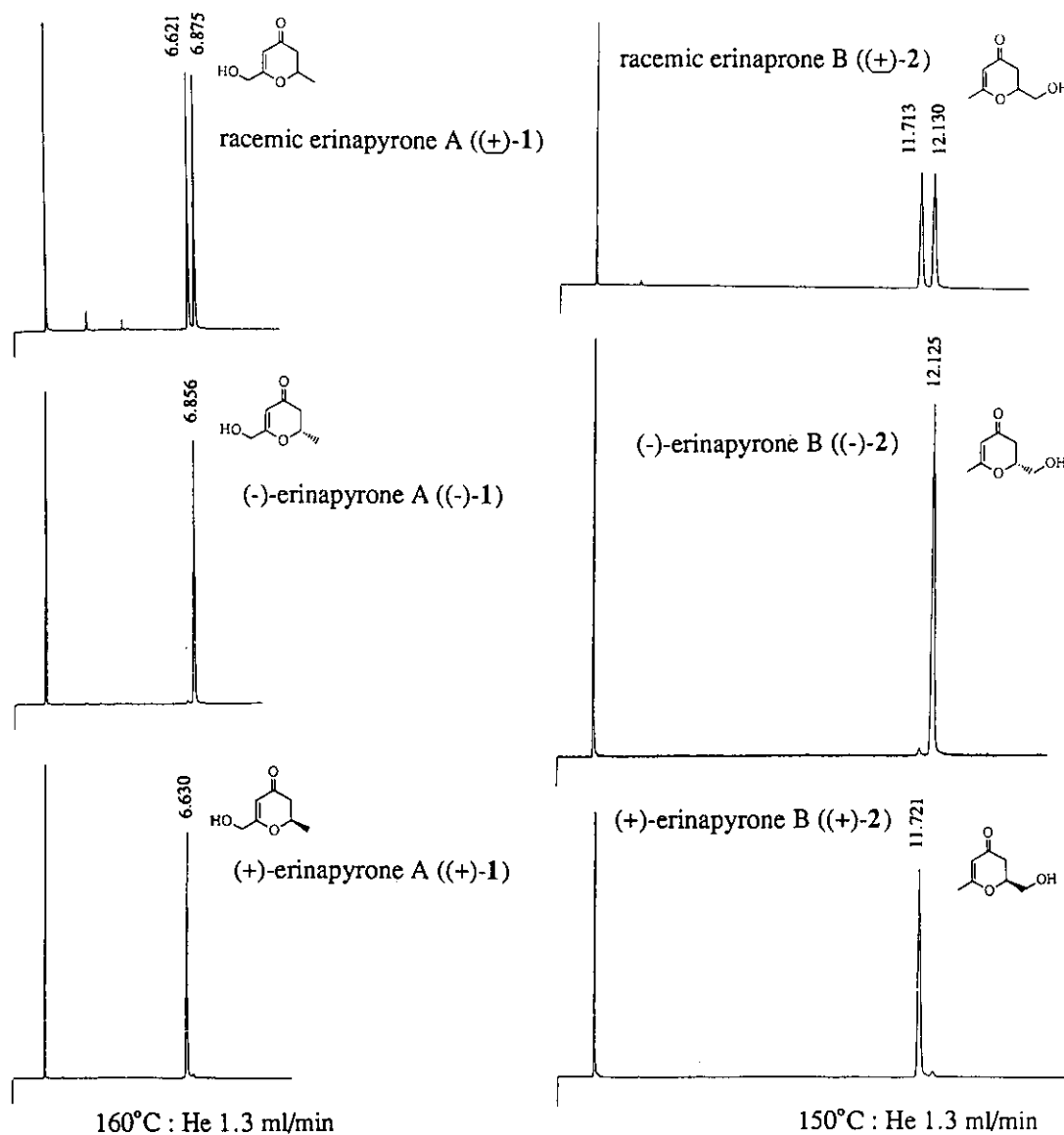


**Scheme 2.** Reagents and conditions: (a) *n*-BuLi, THF, MeI; 96%; (b) *n*-BuLi, THF, (*R*)-benzylglycidyl ether; 56%; (c) HgCl<sub>2</sub>, MeCN, H<sub>2</sub>O; 55%; (d) BF<sub>3</sub>-Et<sub>2</sub>O, DMS, CH<sub>2</sub>Cl<sub>2</sub>; 71%.

The <sup>1</sup>H-, <sup>13</sup>C-nmr, and ir spectra of synthetic (-)-**1** and (-)-**2** completely coincided with those of natural products. However, the specific rotation values of the synthetic (-)-**1**,  $[\alpha]_D^{24} -191.2^\circ$  (c 0.275 CHCl<sub>3</sub>), {lit.,  $[\alpha]_D -74.7^\circ$  (c 0.10 CHCl<sub>3</sub>)<sup>4</sup>} and (-)-**2**,  $[\alpha]_D^{24} -209.6^\circ$  (c 0.177 CHCl<sub>3</sub>), {lit.,  $[\alpha]_D -90.52^\circ$  (c 0.095 CHCl<sub>3</sub>)<sup>4</sup>} have much higher than the reported values of natural products. The racemic erinapyrone A ((+)-**1**), B ((+)-**2**) and unnatural (+)-**1**, (+)-**2** were also synthesized from **5**. The absolute values of the specific rotation values of synthetic (+)-erinapyrone A ((+)-**1**) and (+)-B ((+)-**2**) were approximately the same with those of synthetic (-)-**1** and (-)-**2**: (+)-**1**  $[\alpha]_D^{24} +189.9^\circ$  (c 0.715 CHCl<sub>3</sub>), mp 39-42 °C, (+)-**2**  $[\alpha]_D^{23} +211.3^\circ$  (c 0.214 CHCl<sub>3</sub>), mp 50-53 °C.

In addition, synthetic (-), (+)-erinapyrone A ((-)-1), ((+)-1) and (-), (+)-B((-)-2), ((+)-2) showed high enantiomeric purity on the analysis with chiral gc column for optical resolution (Figure 1).

From the above-mentioned evidence, it has possibility that natural erinapyrones A (1) and B (2) were contaminated by (+)-erinapyrones A ((+)-1) and B ((+)-2).



**Figure 1.** Gas chromatograms of erinapyrones A and B, column: CP-Cycrodextrin-B-236-M-19 (25 m x 0.25 mm i.d. 0.25  $\mu$ m)

## ACKNOWLEDGEMENTS

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## REFERENCES AND NOTES

- 1 H. Kawagishi, R. Shirai, H. Sakamoto, S. Yoshida, F. Ojima, and Y. Ishiguro, *Chem. Lett.*, **1992**, 2475.
- 2 Y. Shizuri, M. Nagahama, S. Yamamura, K. Kawai, N. Kawai, and H. Furukawa, *Chem. Lett.*, **1986**, 1129.
- 3 I. Kubo, T. Matsumoto, D. L. Wagner, and J. N. Shoolery, *Tetrahedron Lett.*, **1985**, **26**, 563.
- 4 H. Kawagishi, personal communication.
- 5 E. J. Corey and D. Seebach, *Angew. Chem.*, **1965**, **77**, 1135 : D. Seebach, N. R. Jones, and E. J. Corey, *J. Org. Chem.*, **1968**, **33**, 300 : A. H. Alberts and D. J. Cram, *J. Am. Chem. Soc.*, **1979**, **101**, 3545.
- 6 K. Fuji, T. Kawabata, and E. Fujita, *Chem. Pharm. Bull.*, **1980**, **28**, 3662.

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