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# Synthesis of Curcumanolide A, a Unique Spirolactone Sesquiterpene[1)]

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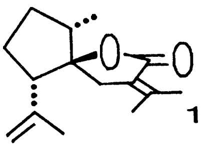
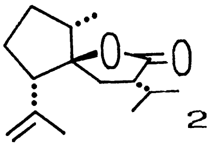
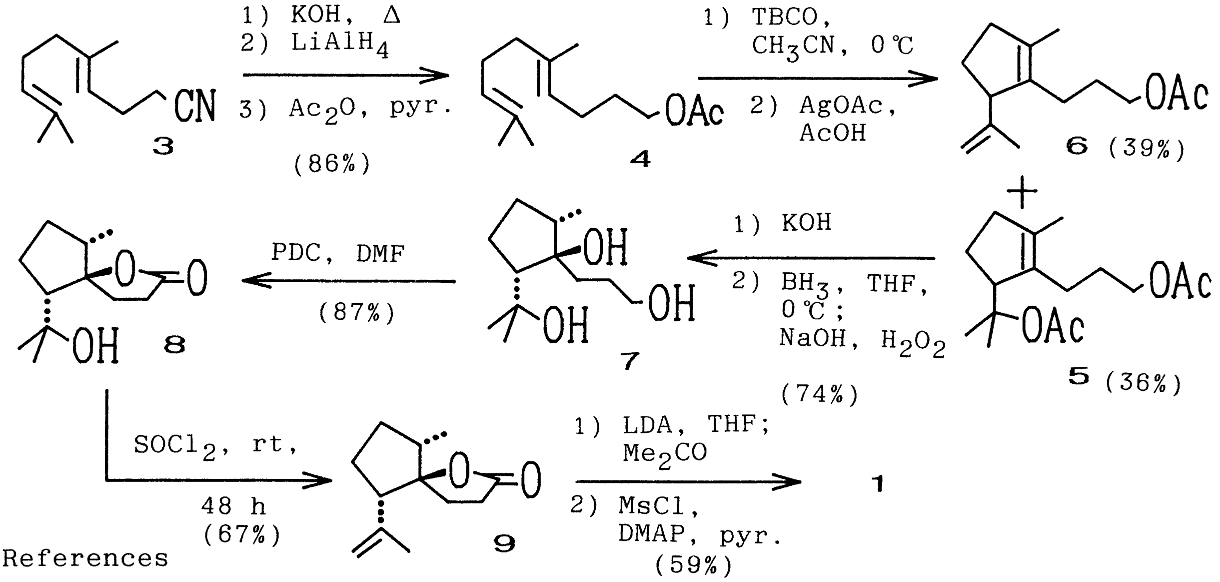
A spirocyclic lactone, curcumanolide A, was synthesized from homogeranyl cyanide in 11 steps in racemic form by using $Br^+$-induced cyclization and subsequent ring contraction method.

Curcumanolide A (**1**) was isolated from the crude drug zedoary and other *Curcuma* species.[2)] Although the zedoary, the dried and ground rhizome of *Curcuma zedoaria* Roscoe has been used medicinally for a long time, **1** had not been examined for medicinal experiment, probably due to the limited amount of the isolated material from natural sources. Its biological activity is, however, sufficiently expected since curcumalactone (**2**), an analogue of **1**,[3)] is reported to exhibit anti-inflammatory activity. For the sake of furnishment of enough materials for the medicinal experiments, we have explored a short step synthesis of these natural products possessing the unique skeleton. Here we describe a racemic synthesis of **1** starting from homogeranyl cyanide (**3**).[4)]


**1**


**2**

The cyanide **3** was hydrolyzed, reduced, and acetylated in usual manners to give bishomogeranyl acetate (**4**) in high overall yield. The cyclization of **4** with 2,4,4,6-tetrabromocyclohex-2,5-dienone (TBCO) in acetonitrile and the subsequent ring contraction with silver acetate yielded the desired 3-[2-(1-acetoxy-1-methylethyl)-5-methylcyclopent-5-enyl]propyl acetate (**5**) (36%) accompanied with diene acetate **6**.[5)] The hydroboration of the hydrolyzed product of **5** with excess borane and successive treatment with alkaline hydrogen peroxide afforded triol **7** stereo- and regioselectively in 81% yield.[6)] The triol **7** was oxidatively cyclized in high yield,[7)] and the resulting hydroxy lactone **8** was dehydrated with thionyl chloride in the absence of pyridine to afford spirolactone **9** in 67% yield accompanied with 9% of regioisomeric isopropylidene product. The synthesis of curcumanolide A (**1**) was carried out in 59% yield by the condensation of the lithium enolate of **9** with acetone followed by the dehydration with methanesulfonyl chloride in pyridine. Physical data except optical rotation of the synthesized compound **1** were identical with those of natural **1**.[8] The detailed biological activity of these synthetic compounds are being examined and will be presented in the near future.



## References

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2)Y. Shiobara, Y. Asakawa, M. Kodama, K. Yasuda, and T. Takeshita, *Phytochemistry*, **24**, 2629 (1985).

3)J. Hu, X. Han, T. Ji, Z. Yang, J. Xie, and Y. Guo, *Kexue Tongbao*, **32**, 816 (1987).

4)E. J. Corey and I. Kuwajima, *Tetrahedron Lett.*, **1972**, 487.

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6)Regioselective hydroboration is clearly caused by the participation of the primary hydroxy group of hydrolyzed product of **5** since no selectivity was observed in the case of silyl ether derivative. Further details of this selectivity will be discussed in a full paper.

7)E. J. Corey and G. Schmidt, *Tetrahedron Lett.*, **1979**, 399.

8)Curcumalactone (**2**) was also synthesized in 30% yield from **9** although the yield is not optimized; the ethylidene derivative of **9** obtained by the condensation of lithium enolate of **9** with acetaldehyde and subsequent dehydration gave racemic **2** and its diastereomer after Michael addition with lithium dimethylcuprate.

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