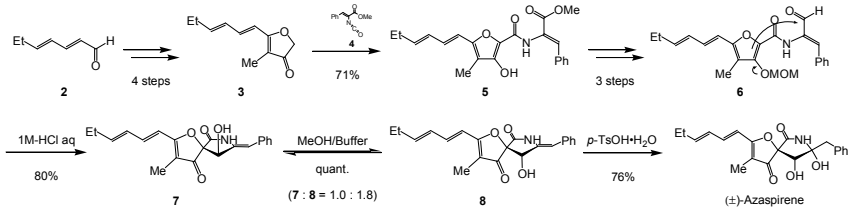
Total synthesis of (±)-azaspirene and racemization in aqueous media.

Takahiro Hasegawa[1], Katuhito Nakazono[1], Kazunori Souma[2], Shun Hirasawa[1], Nobuhiro Kanomata[1,2]

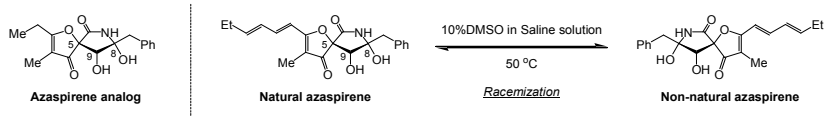
[1]Department of Chemistry and Biochemistry, Waseda University, Shinjuku-Ku, Tokyo, 169-8555, Japan, [2]Department of Applied Chemistry, Meiji University, Tama-Ku, Kawasaki, 214-8571, Japan

(-)-Azaspirene, isolated from the fungus *Neosartorya* sp., is an angiogenesis inhibitor having a characteristic spiro skeleton. Its asymmetric total synthesis was reported independently by two groups.[1] We have been studying synthesis of its natural and non-natural analogs and their in vitro assay.[2] During course of our research we found that the analog readily undergoes racemization of itself in water. Racemization of natural azaspirene, however, has not been announced yet. In this study, we synthesized (±)-azaspirene according to the following scheme and investigated its racemization.

Our synthesis started from commercially available aldehyde **2**. Condensation of furanone **3** and isocyanate **4** followed by transformation of substituents afforded MOM aldehyde **6**. Removing the MOM group induced intramolecular aldol reaction and spiro compound **7** was obtained as a single isomer. Compound **7** was isomerized to **8** in basic conditions and the following hydration afforded racemic azaspirene in good yield.



Racemization of optically active azaspirene, obtained by HPLC separation, was monitored in water. Racemization occurred more slowly than that of the analogous compound. This is probably because hydrogen bond between a hydroxyl group at C-8 and a carbonyl group of dihydrofuranone moiety is stronger in natural azaspirene due to longer conjugation with a hexadienyl side chain.



1 (a) Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 12078-12079. (b) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1703-1716.

2 Emoto, M.; Yano, K.; Choijamts, B.; Sakai, S.; Hirasawa, S.; Wakamori, S.; Aizawa, M.; Nabeshima, K.; Tachibana, K.; Kanomata, N. *Anticancer Res.* **2015**, *35*, 2739-2746.