

Strategic Young Researcher Overseas Visits Program
for Accelerating Brain Circulation 2011

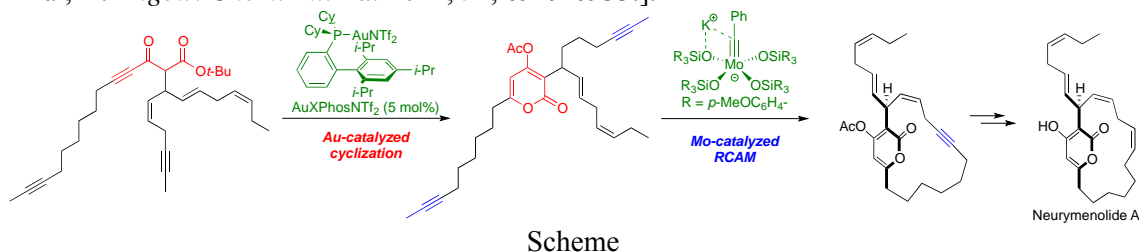
**“Development of Young Researchers
Based on International Joint Research
on Green Energy Systems”
Progress Report**

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3. Host Institution: Max-Planck-Institut für Kohlenforschung
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4. Host Researcher: Professor Alois Fürstner
5. Duration: 10-July-2012 – 12-July-2013
6. Research Topic:
Development of an atom-economical and energy-saving methodology for
effective synthesis of highly functional chemical
compounds
7. Overview of the Results of the Collaborative Research:

Marine natural products derived from a variety of sources have attracted considerable attention from chemists for their unusual structures and concomitant biological activities. Therefore, a large number of methodologies for the syntheses of them have been reported so far. On the other hand, the total synthesis of marine natural products possessing a macrocyclic pyrone scaffold was given exceptionally little attention despite of their unique structures and potent biological activities. The aim of this research is to develop an

atom-economical and energy-saving methodology for effective synthesis of highly functional chemical compounds such as naturally occurring pyrone-type macrocycles. Thus, we chose a marine natural product possessing a macrocyclic ring with 4-pyrone moiety as a target and attempted its total synthesis.

Recently, Professor Dr. Alois Fürstner and co-workers have found that a certain type of molybdenum complex effectively catalyzes the ring-closing alkyne metathesis (RCAM) reaction. Furthermore, they have also developed the gold-catalyzed construction of 2-pyrone from 3-oxopent-4-ynoates. By using these reactions, the total synthesis of 2-pyrone macrocycle neurymenolide A was successfully achieved (Scheme) [W. Chaładaj et al, *A. Angew. Chem. Int. Ed.* **2012**, *51*, 6929-6933.].



Based on the previous results, we initially carried out the retrosynthetic analysis of the target molecules by using molybdenum-catalyzed RCAM and gold-catalyzed pyrone synthesis as key reactions. As a result, it seemed that the target molecule could be synthesized from a carboxylic acid part (fragment A) and an alcohol part (fragment B).

According to the retrosynthetic analysis, the synthesis of the fragment A was examined. The fragment A could be synthesized from commercially available 1,7-octadiyne in five steps. On the other hand, synthesis of the fragment B was rather problematic owing to its instability. After several attempts, we could obtain the desired fragment B by using ring-opening reaction of epoxide, P-2 Nickel mediated semi-reduction, and Corey-Fuchs olefination as key reactions.

Having established the synthesis of fragment A and B, we next attempted the construction of the macrocyclic scaffold using gold and molybdenum catalyzed reactions. Thus, fragment A and B were coupled using conventional esterification. Gold-catalyzed reaction of the resulting ester proceeded smoothly to produce pyrone. Successive molybdenum catalyzed ring closing alkyne metathesis (RCAM) afforded the macrocyclic compound in good to excellent yield.

At present, we are still attempting to synthesize the target natural product. Therefore, we will publish these results after completion of the total synthesis.

8. Deployment Plans for Future Collaborative Research:

We could find that molybdenum-catalyzed RCAM and gold-catalyzed pyrone synthesis are effective method for construction of macrocyclic pyrone framework. Thus, we will apply the method to the synthesis of the other macrocyclic pyrone type natural products.

9. List of Collaborative Research Progress:

At present, we are still attempting to synthesize the target natural product. Therefore, we will publish these results after completion of the total synthesis.