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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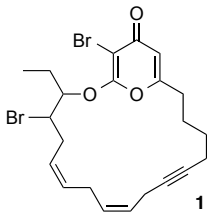
5. Duration: 10-July-2012 – 12-July-2013

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 4-pyrone-type macrocycles. Thus, we chose a marine natural product **1** possessing a macrocyclic ring with 4-pyrone moiety as a target and attempted its total synthesis.



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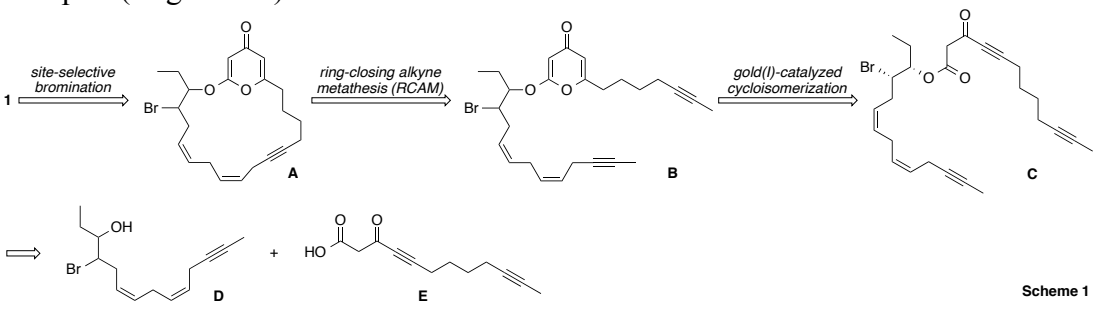
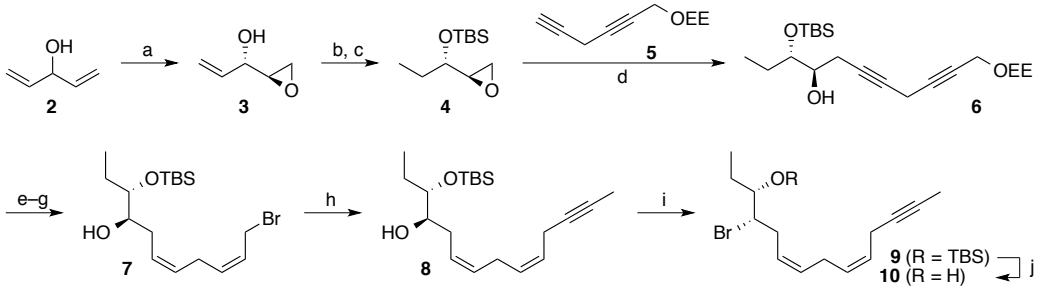
Recently, Professor Dr. Alois Fürstner and co-workers have found that a certain type of molybdenum complex effectively catalyzes the ring-closing alkyne metathesis (RCAM) reaction. Furthermore, they have also developed the gold-catalyzed construction of 2-pyrones from 3-oxopent-4-ynoates. By using these reactions, the total synthesis of 2-pyrone macrocycle neurymenolide A was successfully achieved [*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 (Scheme 1). As a result, it seemed that the target molecule could be synthesized from an alcohol part (fragment D) and a carboxylic acid part (fragment E).



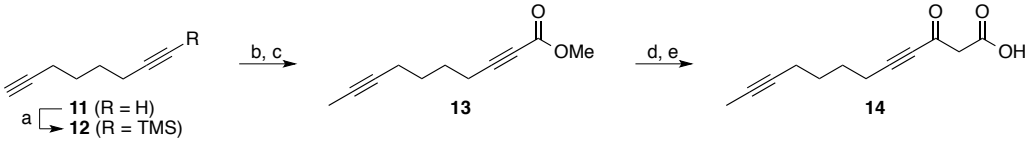
Scheme 1

According to the retrosynthetic analysis, synthesis of the fragment D was examined. After several attempts, we could obtain the desired fragment D by using ring-opening reaction of epoxide **4**, P-2 Nickel mediated semi-reduction, and copper-mediated nucleophilic substitution as key reactions (Scheme 2).



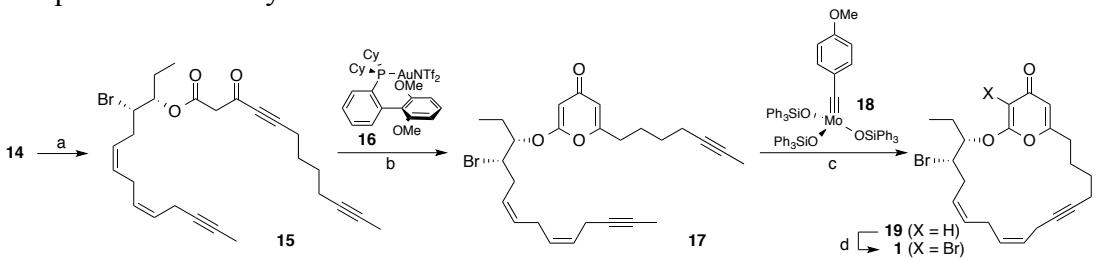
Scheme 2. (a) Ti(O*i*-Pr)$_4$ (10 mol%), (+)-diisopropyl tartrate (13 mol%), cumene hydroperoxide, CH_2Cl_2, MS 4 Å, –25 °C (82%); (b) TBSCl, imidazole, DMF, 0 °C → RT (90%); (c) H_2 (1 atm), Pd/C (10 mol% Pd), EtOAc (95%); (d) (i) **5**, *n*-BuLi, THF, –78 °C; (ii) $BF_3{\cdot}OEt_2$, then **4**, –78 °C (72%); (e) PPTS, MeOH, 30 °C (98%); (f) H_2 (1 atm), P2-Ni (25 mol%), EtOH (79%); (g) CBr_4, PPh_3, CH_2Cl_2, 0 °C (91%); (h) propynylmagnesium bromide, CuI (50 mol%), THF, –15 °C → –10 °C (81%); (i) CBr_4, PPh_3, toluene, 65 °C (60%); (j) HF·pyridine, THF, 0 °C (83%).

On the other hand, fragment E could be synthesized from commercially available 1,7-octadiyne **11** in five steps (Scheme 3).



Scheme 3. (a) LiHMDS, THF, –78 °C, then TMSCl, –78 °C → RT (52%); (b) *n*-BuLi, THF, –78 °C, then MeI, –78 °C → RT (91%); (c) MeLi, THF, –78 °C, then $ClCO_2Me$, –78 °C → 0 °C (86%); (d) *t*-BuOAc, LDA, –78 °C, then **21** (87%); (e) TFA, CH_2Cl_2 (99%).

Having established the synthesis of fragment D and E, we next attempted the construction of **1** *via* the macrocyclic scaffold using gold and molybdenum catalyzed reactions (Scheme 4). Thus, fragment D and E were coupled using conventional esterification. Gold-catalyzed reaction of the resulting ester proceeded smoothly to produce 4-pyrone **17**. Successive molybdenum-catalyzed RCAM afforded the macrocyclic compound **19** in good yield. After site-selective bromination, we have completed the total synthesis of **1**.



Scheme 4. (a) **10**, DCC, DMAP cat., CH_2Cl_2, 0 °C (70%); (b) **16** (3 mol%), MeCN/HOAc (4:1) (97%); (c) **18** (5 mol%), MS 5 Å, toluene (82%); (d) NBS, THF (40%).

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:

Publication(s)

1. L. Hoffmeister, T. Fukuda, G. Pototschnig, and A. Fürstner, "Total Synthesis of an Exceptional Brominated 4-Pyrone Derivative of Algal Origin: An Exercise in Gold Catalysis and Alkyne Metathesis," *Chemistry - A European Journal*, **21** (12), 4529-4533 (2015).