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海外特別研究員最終報告書

独立行政法人日本学術振興会 理事長　殿

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受付番号　201960708
氏　　名　奥村美樹子
（氏名は必ず自署すること）

海外特別研究員としての派遣期間を終了しましたので、下記のとおり報告いたします。
なお、下記及び別紙記載の内容については相違ありません。

記

1. 用務地（派遣先国名）用務地：　バークレー　（国名：　米国　）

2. 研究課題名（和文）※研究課題名は申請時のものと違わないように記載すること。
新規抗生物質骨格の探索：ブロモスファエロンおよび類縁体の全合成と生物活性評価

3. 派遣期間：　令和　1 年　7 月　2 日　～　令和　3 年　7 月　1 日

4. 受入機関名及び部局名
受入機関名：　カリフォルニア大学バークレー校
部局名：　化学科

5. 所期の目的の遂行状況及び成果…書式任意　**書式任意（A4 判相当 3 ページ以上、英語で記入も可）**
（研究・調査実施状況及びその成果の発表・関係学会への参加状況等）
（注）「6. 研究発表」以降については様式 10－別紙 1～4 に記入の上、併せて提出すること。

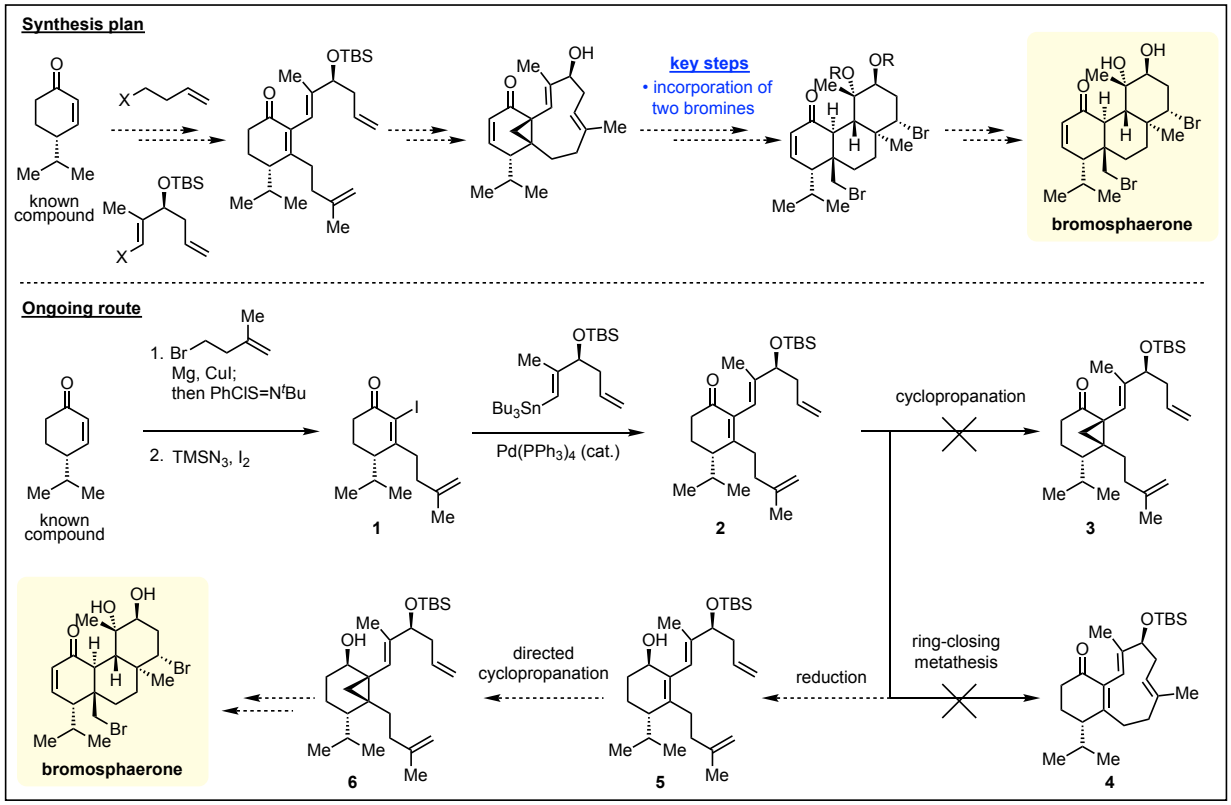
Progress towards the synthesis of bromosphaerone

The golden age of antibacterial research during the mid-20th century witnessed the discovery of many highly potent antibiotics from natural sources. However, overestimation of the utility of these therapeutics, both in academia and the pharmaceutical industry, have failed to address the forthcoming rise of pathogenic bacteria resistant to these known antibiotics. As a result, previously treatable infections are now becoming life-threatening diseases. Traditional approaches to this crisis through semisynthetic modifications of the conventional classes of antibiotics has met very limited success over the past few decades. Thus, identification of novel bioactive chemotypes from unexplored small molecules in nature is imperative for the long-term success of modern medicine. Total synthesis, the creation of entire natural products and their analogues from simple building blocks, could offer one of the most straightforward means to this end, as the synthesis could not only deliver sufficient supply of the material to be analyzed, but could also produce any conceivable structural alteration for improved potency.

Bromosphaerone is a complex marine algae-derived bromoditerpenoid with promising antibacterial activity against Gram-positive bacterium species *S. aureus*.[1] Despite its promising bioactivity and the structural features, however, this compound has never been synthesized, and no further biological investigation have been reported. Thus, in order to thoroughly investigate bromosphaerone and its analogues for their potential pharmaceutical usage, we first seek to establish a concise and scalable enantioselective synthetic pathway for the bromosphaerone. Our synthesis plan is depicted in Scheme 1 top. In order to install two sensitive alkyl bromide moieties effectively, we decided to construct the core carbon skeleton first, then install other heteroatom functionalities. At later stage, we plan to incorporate the two alkyl bromides through bromide-mediated cyclopropane ring-opening and biomimetic bromination/cyclization[2].

As shown in Scheme 1 bottom, we have commenced our synthesis from a simple and known enone compound and performed 1,4-addition of the side chain as well as oxidation under Mukaiyama conditions to reinstall the unsaturation to obtain vinyl iodide **1**. A variety of conditions were investigated to introduce the other side piece on to the iodide **1** through transition metal-catalyzed cross-coupling reactions, and this has been realized by Stille

Scheme 1: Progress towards synthesis of bromosphaerone



coupling using the corresponding vinyl tin species. With tetraene **2** in hand, we then explored conditions to install cyclopropane moiety onto the enone. Despite numerous attempts, this transformation was not achieved under any conditions tested, most likely due to unfavorable steric effects. We then shifted our gear towards the formation of 10-membered ring through ring-closing metathesis. Although we have screened many of the well-known catalysts based on ruthenium complexes, we could not observe any desired macrocycle. This may be because of the high degree of unsaturation within the ring system, which also resulted in the undesired olefin isomerization and decomposition of the material. We thought these problems could be solved by converting the some of the unsaturated structures to their corresponding saturated species. To this end, we are looking into reduction of the carbonyl species in tetraene **2**, which is anticipated to proceed stereoselectively, and use this allylic alcohol as a handle to promote directed cyclopropanation. With compound **6**, we will then retest the ring-closing metathesis to form our macrocycle, and further proceed with our synthesis.

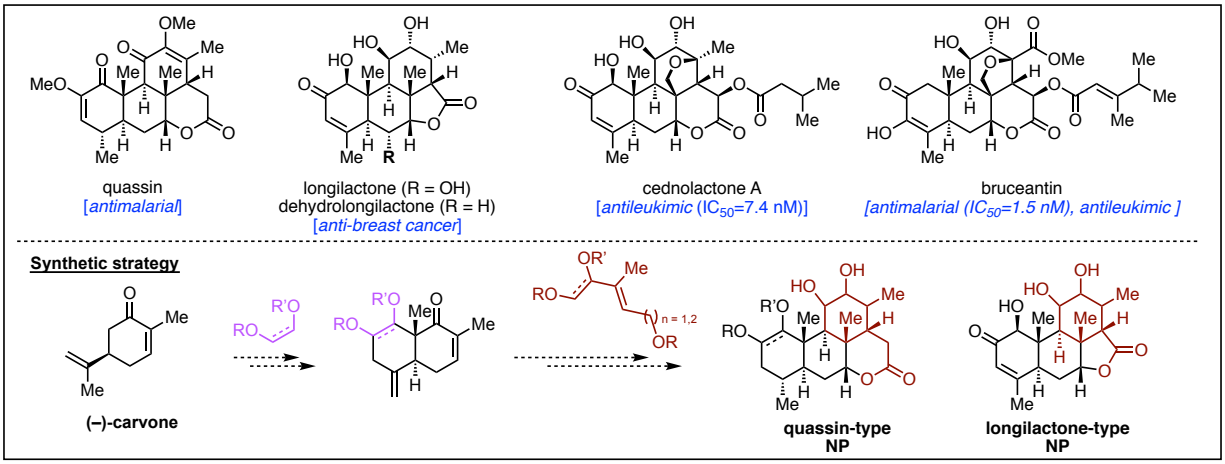
Progress towards the synthesis of quassinoid natural products

In addition to the exploration to the synthesis of bromosphaerone, I was also involved in a project based on the synthesis of quassinoid natural products. This opportunity was presented to me by Prof. Maimone, where this target has been long standing challenge in this group, as well as the scientific community.[3]

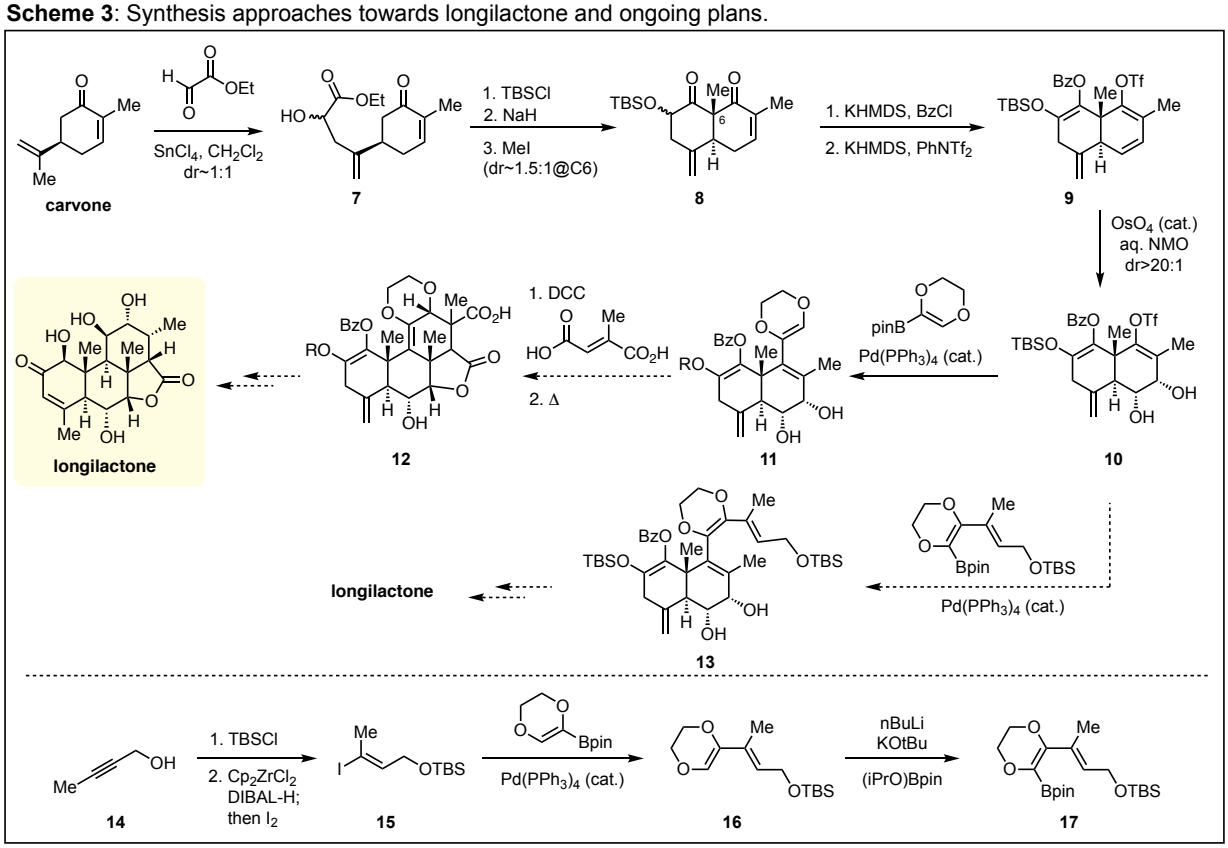
Quassinoids are a family of degraded triterpenes with a rich history in traditional medicine, and are especially noted for their anti-malarial, anti-viral (HIV), anti-leukemic, and potent cytotoxic properties (representative compounds shown in Scheme 2 top).[4] Despite the promising bioactive features of these compounds, typical reported synthetic pathways require >20 chemical steps with minimal material obtained, which significantly hampers the studies towards medicinal applications. To this end, we have devised a divergent synthetic plan that could greatly shorten the synthesis of these highly bioactive compounds from commercially available chiral building blocks, carvone (Scheme 2 bottom). The success of our expedient synthesis relies on the use of highly oxygenated pieces to be coupled onto the core carvone, which also imposes a great challenge due to its high reactivity and instability.

We chose longilactone as our first target and begun our synthetic approach with the formation of A ring (left ring, Scheme 3). Upon screening a variety of 2-carbon-synthons bearing oxygen functionality, we found that the Sn-mediated ene-reaction between carvone and ethyl glyoxalate worked remarkably to provide ester **7**. Although the reaction proceeded with 1:1 diastereoselectivity, we carried both materials forward as a mixture since we plan to oblate the stereochemistry later. Silyl protection of the resulting alcohol moiety, followed by intramolecular enolate acylation and methylation furnished diketone **8**; we have a preliminary result that these 4-step sequence could be

Scheme 2: Representative quassinoid natural products and synthetic plans.



Scheme 3: Synthesis approaches towards longilactone and ongoing plans.



performed in only two steps. Although diastereoselectivity at C6 is only moderate, all diastereomers could be easily separated by column chromatography. Then, double enolization/trapping sequences delivered vinyl triflate **9**, a process which could also be telescoped into a single operation. The vinyl triflate group would later serve as a functional handle to install the requisite side piece for the formation of C- and D-ring. At this point, we tested some conditions to selectively install oxygen functionalities at the olefin moiety at C9 and C10 positions, in the presesce of three other reactive olefins. Gratifyingly, dihydroxylation using OsO_4 as a catalyst proceeded with high chemo- and stereoselectivity to provide the desired vinyl triflate **10**.

We then turned our attention to the coupling of vinyl triflate **9** and scaffolds appropriate for the formation of C- and D-ring of longilactone. We chose dioxene and its derivatives as our coupling partner and examined conditions to install this functionality. Using dioxene as the nucleophile and through intense optimizations of the reaction conditions, we found that Suzuki-Miyaura cross-coupling of triflate **10** with dioxeneboronic acid pinacol ester proceeded smoothly and cleanly to give the diene **11** in high yield. Other similar transformations such as Stille coupling and Kumada coupling with corresponding dioxene-based nucleophiles failed to provide the same product. With the diene **11** in hand, we then attempted to install the remaining motif selectively to the allylic alcohol moiety, and then further carry the product forward for the thermal Diels-Alder reaction to forge both C-ring and the D-lactone ring at the same time. This acylation turned out to be very challenging, as the product readily decomposed presumably through the effect of the conjugated electron rich dioxene group. With minimal acylated product obtained, we tested the Diels-Alder reaction; however, we have not been able to isolate the desired pentacycle **12**, and further efforts to improve this sequence is ongoing.

Alternatively, we have synthesized another dioxeneboronic acid pinacol ester bearing all necessary carbons (Scheme 3 bottom). In this way we could eliminate the unproductive acylation step and expedite our synthesis. The synthetic sequence for compound **17** went straightforward from the propargyl alcohol **14**, which was converted to vinyl iodide **15**, followed by cross-coupling with dioxeneboronic acid pinacol ester to give diene **16**. Then the boronic acid picnacol ester moiety was install by selective deprotonation and borylation. With the resulting coupling partner

17, we are currently exploring the conditions to couple together with vinyl iodide **9** and further apply the product to electrocyclization reaction to form the C-ring, then achieve the formation of 5-memeberd lactone ring. Further investigation will then be carried out to completion of the synthesis of longilactone. Upon finishing the synthesis, we are planning to expand our route to other compounds in the quassinoid natural products, as well as conduct some bioactivity studies.

References

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