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Novel synthesis of zerumbone-pendant derivatives and their biological activity

Takashi Kitayama [a,*], Maki Nakahira [a], Kae Yamasaki [a], Hiromi Inoue [a], Chika Imada [a], Yuji Yonekura [a], Masataka Awata [a], Hikaru Takaya [b], Yasushi Kawai [c], Kohta Ohnishi [d], Akira Murakami [d]

[a] Department of Advanced Bioscience, Graduate School of Agriculture, Kinki University, Nara 631-8505, Japan
[b] Institute for Chemical Research, Kyoto University, Uji 611-0011, Japan
[c] Nagahama Institute of Bio-Science and Technology, Nagahama, Shiga 526-0829, Japan
[d] Division of Food Science and Biotechnology, Graduate School of Agriculture, Kyoto University, Kyoto 606-8502, Japan

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ABSTRACT

Zerumbone **1**, having powerful latent reactivity and containing two conjugated double bonds and a double conjugated carbonyl group is the major component of the essential oil of wild ginger, *Zingiber zerumbet* Smith. The conjugation system plays an important role in the expression of biological activity. *N*-Bromosuccinimide (NBS) reaction of **1** gave high reactive intermediate **2** with an *exo*-methylene group, which was obtained from **1** quantitatively. Treatment of **2** with nucleophiles gave various zerumbone-pendant derivatives, including C–H, C–O, C–N, and C–C bond formation, maintaining the conjugation system through S_N2'-type reaction. Almost all zerumbone-pendant derivatives showed a good value of IC_{50} against the suppressive effect of NO generation. Among them, amine derivative **5**, binding with 2 mol of zerumbone, showed the strongest activity (IC_{50}: 0.24 μM).

1. Introduction

Zerumbone **1**[1] is a cyclic sesquiterpene and potential resource for natural materials-related diversity-oriented synthesis '*NMRDOS*'.[2] Compound **1**, having powerful latent reactivity and containing three double bonds, two conjugated and one isolated, and a double conjugated carbonyl group in an 11-membered ring structure, is a monocyclic sesquiterpene found as the major component of the essential oil of wild ginger, *Zingiber zerumbet* Smith. Zerumbone as a natural resource showed attractive reactivity and could be converted into various structures;[2–11] for example, transannular,[3–5] ring contracting skeletons,[3,4] asymmetric syntheses,[6–11] etc.[2] For example, our discovery of a double Favorskii rearrangement via 2,3-dibromozerumbone was an attractive novel reaction and bromine was added to 2,3-position in the double conjugated system at the initial step.[3] Not only does zerumbone shows attractive reactivity, but it also has a broad array of important biological activities; for example, anti-inflammatory,[12] antitumor,[13] anticancer,[14] and anti-HIV.[15] Moreover, zerumbone derivatives also exhibited useful biological activities.[16] However, it has been shown that the conjugation system of zerumbone plays an important role in the expression of almost all of its biological activities.[12c,e,14b] If it is easy to form zerumbone derivatives maintaining the conjugation system without a reaction on the system, the derivative will not only be able to be used as a tool to elucidate the mechanism of biological activity, but will also be developed as a medicine with stronger effect. As shown in Scheme 1, however, the reactivity of the double conjugated system of zerumbone was quite high and it is very difficult for other parts of zerumbone to convert into the derivatives maintaining the conjugation system. Previously, we showed two examples that reacted just on the isolated olefin without a reaction on the conjugation system, as shown in Scheme 1,[2–5] although the subsequent reaction maintaining the conjugation system is very difficult.

The reaction of **1** with NBS gave the highly reactive intermediate **2**, which could realize our target. We report here that zerumbone reacted with NBS to afford a substantial intermediate **2** and the subsequent reaction of **2** gave the desired zerumbone-pendant derivatives maintaining the conjugation system. One of the zerumbone derivatives showed stronger inhibition of NO generation by endothelial cells than zerumbone.

* Corresponding author. Fax: +81 742 43 8976; e-mail address: kitayama@nara.kindai.ac.jp (T. Kitayama).

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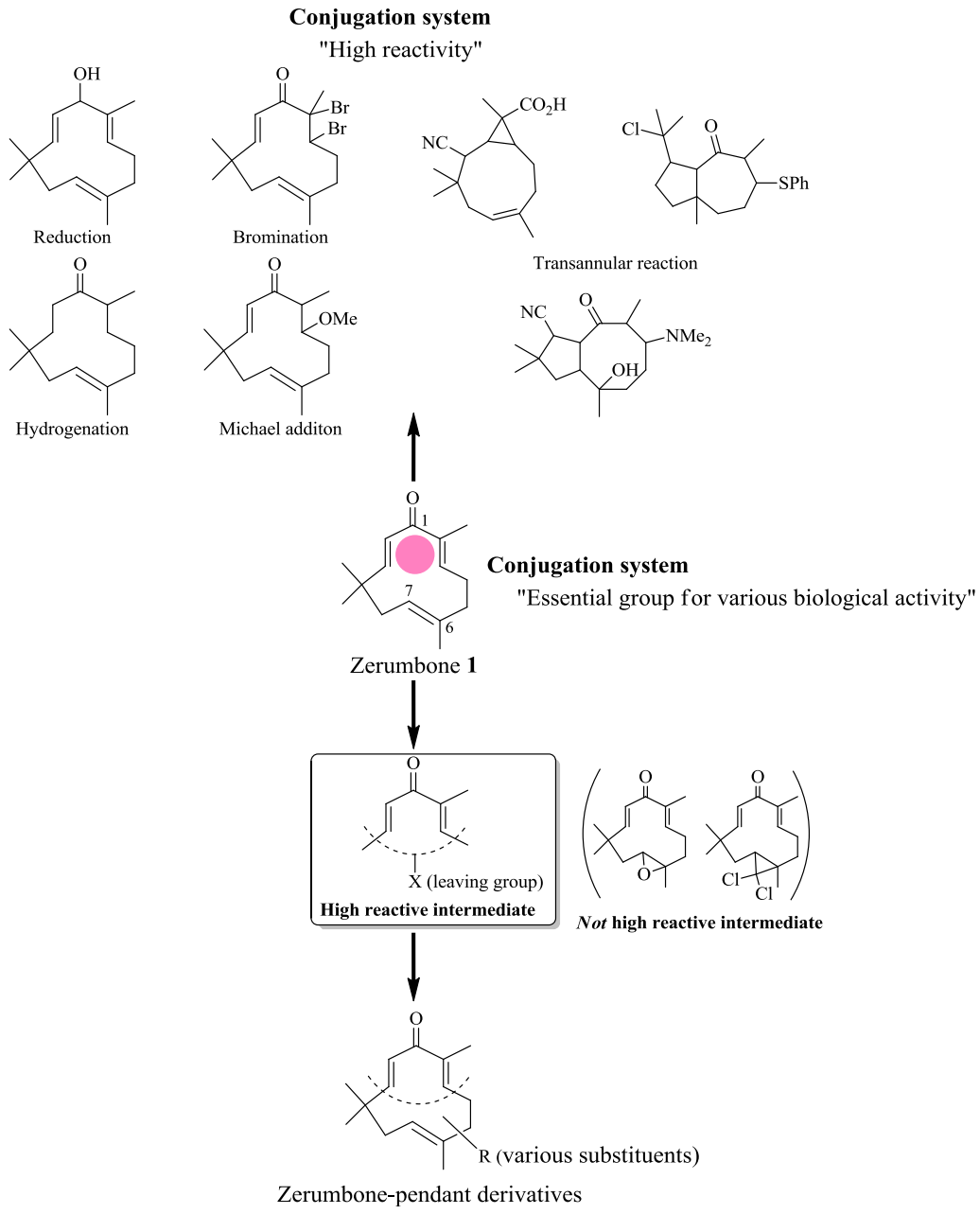

Scheme 1.

2. Results and discussion

On treatment with bromine in carbon tetrachloride[3] or $KBrO_3$ aqueous system, zerumbone was converted to 2,3-dibromozerumbone in high yield, as shown in Scheme 2. This result means that a bridgehead bromonium ion is formed on C2 and C3 first; therefore, the bromonium ion is the activated species in the reaction system. Since NBS behaves as a source of bromonium ion in the aqueous system in general,[17] bromohydroxylation at C2 and C3 must be occurred by an NBS reaction with zerumbone under aqueous conditions. However, on treatment with NBS at room temperature, zerumbone was converted to **2** with a bromine at C7 and an *exo*-methylene group at C6 after allylic rearrangement. Thus, bromo radical as an activated species was involved in this reaction without radical initiator. Since zerumbone **1** seems to show stable SOMO energy at its 6-methyl and 7-carbon positions using Gaussian 03, UB3LYP/6-31G, radical species should be reacted at this position.

However, **2′** was not produced at all under this condition although a difference in reactivity between 6-methyl carbon and C7 was hardly observed in the calculation. At least, it is very interesting that zerumbone might promote the production of bromo radical.

As shown in Table 1, particularly in the CH_3CN and H_2O (1:1) system at room temperature for 1 min, **2** was obtained quantitatively and rapidly (entry 3). Then H_2O was poured into the solution, filtrated immediately, and washed with H_2O several times to afford **2** conveniently. When the reaction time was prolonged over 1 min, **2** was decomposed immediately (entry 4). Perhaps, further bromination might proceed on allylic position and olefin after generation of **2**. In other solvents, the reaction velocity was delayed or began to decompose (entries 1, 2, 4–9).