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Novel cleavage of (*E*)-allyl *vic*-diols to aldehydes using the 2nd-generation Grubbs catalyst

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ABSTRACT

Secondary (*E*)-allyl *vic*-diol cleavage in the presence of the 2nd-generation Grubbs catalyst has been developed. The position of a *vic*-diol adjacent to C=C plays a crucial role in the cleavage reaction compared to an alkyl *vic*-diol based on a model compound.

Symbiodinolide (**1**, Fig 1) can be classified as super-carbon-chain compound (SCC)[1] with a molecular weight of 2859. Recently, its isolation, structure elucidation, and biological activities were reported.[2] However, many configurations of stereocenters in the polyunsaturated 62-membered macrolactone are not yet clear. Since stereochemical assignments could not be completed by spectral analysis, we carried out degraded reactions such as effective ethenolysis[3] as described before.[2] In the course of ethenolysis, we found a new type of oxidative cleavage reaction. We describe herein a novel cleavage reaction of symbiodinolide itself and model compounds.

First, we attempted to carry out ethenolysis (olefin cross-metathesis with ethene) of symbiodinolide (**1**) with the 2nd-generation Hoveyda-Grubbs catalyst[4] (**2**, Fig. 2), and three degraded fragments with a terminal olefin were obtained from the 62-membered lactone (Scheme 1). For assignment of the absolute stereochemistries at C3, C5, C6, and C7, we successively carried out methanolysis to gain a seco ester[5] of symbiodinolide (**1**, Fig. 1), and then performed ethenolysis with the 2nd-generation Grubbs catalyst[6] (**3**, Fig. 2) to obtain fragment C1–C9 or C11 with a terminal olefin. Unexpectedly, the position of the 13,14-diol underwent cleavage to give two α,β-unsaturated aldehydes, C1–C13 and C14–C25′ (Scheme 2). However, ethenolysis is a unique unsaturated rearrangement of carbon–carbon bonds in the presence of metal carbene complexes.[7] With the advent of powerful Ru-based catalysts such as the 2nd-generation Grubbs catalyst (**3**), the number of applications of this reaction has dramatically increased over the past few years. Thus far, however, there has been no report of the cleavage of allyl *vic*-diol by Grubbs II (**3**) catalyst detected.

To clarify the validity and reliability of this new cleavage of (*E*)-diallyl *vic*-diol by Grubbs II (**3**) and to evaluate the reaction condition, the above reaction was performed with a commercially available model compound, hydrocinnamoin (**4**, Table 1). The results of the investigation are summarized in Table 1. In the oxygen-free case, hydrocinnamoin (**4**) was cleaved into benzenepropenal (**5**) in 94% yield with Grubbs II (1 equiv) under ordinary ethene pressure (balloon) for 4 h at room temperature. This result was consistent with the ethenolysis of symbiodinolide (**1**) by Grubbs II (entry 1 and Scheme 2).

The catalytic cleavage of *vic*-diol to aldehydes with O_2 by Ru complex had been reported previously,[8] and therefore we tested the cleavage of (*E*)-diallyl *vic*-diol, hydrocinnamoin (**4**), under ordinary air pressure (entry 2). Benzenepropenal (**5**) was obtained in 79% yield as in the oxygen-free condition (entry 1).

We also examined the correlation between of Grubbs II (**3**) and the amount of product for this new cleavage reaction. With 0.1 equiv of Grubbs II under oxygen-free and ordinary ethene pressure (balloon) for 4 h at room temperature, only a small amount of compound **5** was obtained. Similar result was obtained under an atmosphere of room air (entries 3 and 4). Next, we prepared mono-allyl *vic*-diol (**6**) from **4** (Table 1), and investigated the cleavage of **6** using Grubbs II in the same reaction conditions (entry 1), but only small amounts of **5** and benzenepropanal **7** were obtained. However, **5** and **7** were formed in 33% yield with 2 equiv of catalyst (**3**, entries 5 and 6). Further, with 5 equiv of Grubbs II,

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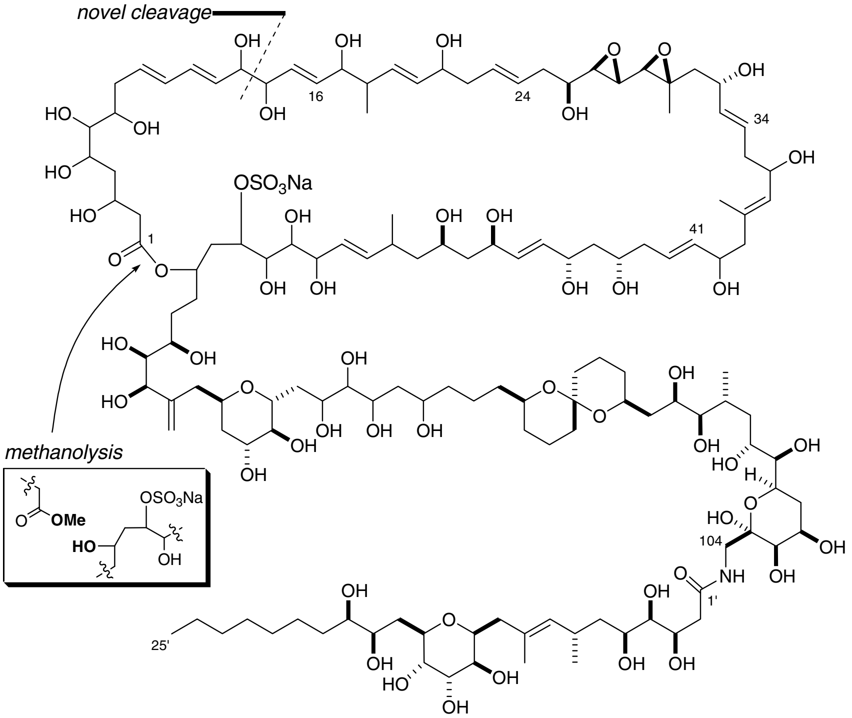

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Figure 1. Structure of symbiodinolide (**1**).

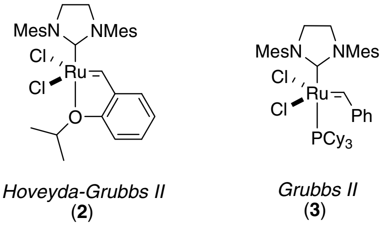
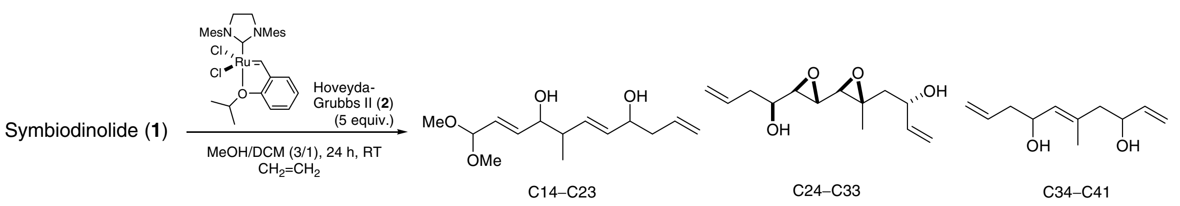


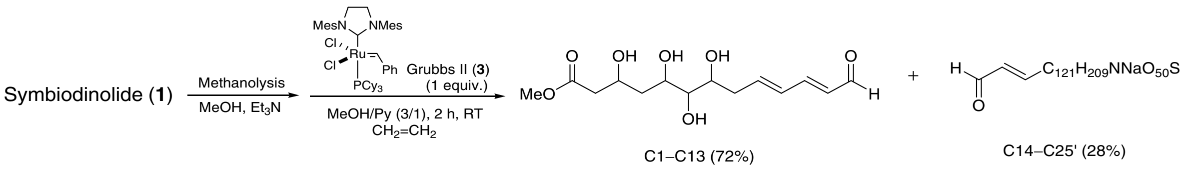
Figure 2. Structures of olefin cross-metathesis catalysts Hoveyda-Grubbs II (**2**) and Grubbs II (**3**).

the starting material (**6**) was not found (data not shown). Finally, we used alkyl *vic*-diol (**8**, Fig. 3) derived from **4**, but the degraded compound **7** was not formed. Meanwhile, we investigated the effect of solvent in this cleavage reaction with MeOH/DCM, and a high yield of **5** was consistent with entry 1. We also tried this degradation reaction of cyclic system with a commercially available compound D-glucal in the same reaction conditions (entry 1), however, the reaction did not work. These results indicated that the cleavage of allyl *vic*-diol depended on the amount of Grubbs II, but not O_2, and that the position of *vic*-diol adjacent to C=C plays a crucial role in the cleavage reaction. A diallyl *vic*-diol structure gives a higher yield than mono-allyl *vic*-diol structure at a low concentration of Grubbs II (1 equiv), and the allylic system could be essential for this reaction. In addition, the degraded acetal fragment C14–C23 of symbiodinolide (**1**, but not the terminal olefin at C16) suggested that diallyl *vic*-diol cleavage could also arise from Hoveyda-Grubbs II (**2**, Scheme 1).

In conclusion, we have developed a new convenient methodology for allyl *vic*-diol selective cleavage by Grubbs II (**3**).[9] It uses



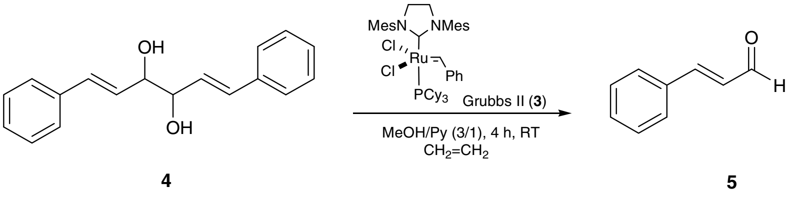
Scheme 1. Ethenolysis of symbiodinolide (**1**) by Hoveyda-Grubbs II (**2**).

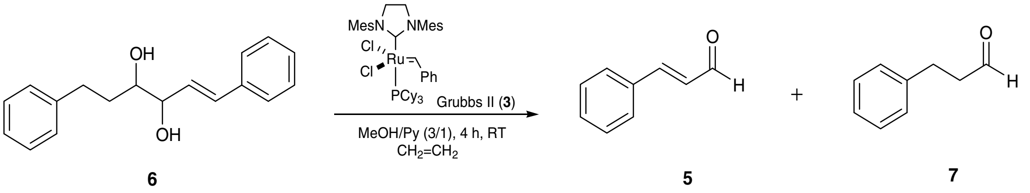


Scheme 2. Novel cleavage of (*E*)-diallyl 13,14-diol in symbiodinolide (**1**) by Grubbs II (**3**).

Table 1

Cleavage of (*E*)-di-, or mono-allyl *vic*-diol to the corresponding aldehyde with Grubbs II (**3**)





Entry	Grubbs II (equiv)	O_2	Yield of **5**[a] (%)	Ratio of **5**:**6**:**7**[b]
1	1	None	94	
2	1	1 atm	79	
3	0.1	None	6	
4	0.1	1 atm	11	
5	1	None		10:80:10
6	2	None		33:34:33

[a] Yields were obtained based on a quantitative analysis by HPLC.

[b] The ratio was determined based on ^{1}H NMR analysis.

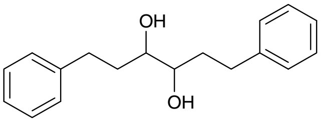


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Figure 3. 3,4-Hexanediol,1,6-diphenyl (**8**).

only commercially available reagents at small amount (in the case of symbiodinolide: $0.9/_{1\,\mathrm{equiv}}$–$3.5/_{5\,\mathrm{equiv}}$ mg) in the degradation reaction of the hard-won natural product, and proceeds easily under comparatively mild reaction conditions, such good stability toward oxygen, and a short reaction time (2 h) at room temperature. This strategy is very useful to stereostructural analysis in natural products chemistry. Because of this selective cleavage of allyl *vic*-diol in polyene alcohol compound can afford the simple products, namely, two corresponding aldehydes, compared with the complicated mixtures using known unselective *vic*-diol cleavage (e.g., periodic acid), and the stereochemical determination of the degraded fragments could be completed. Further studies, particularly on the acyclic *Z*-isomer experiment and the reaction mechanism are now underway.[10]

Acknowledgments

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9. This new allyl *vic*-diol cleavage differs from Ishii's cleavage reaction reported as Ref. 8a. The reasons are as follows: (a) the significance of this new cleavage reaction is a selective cleavage for allyl *vic*-diol, but not a general 1,2-diol cleavage reported by Ishii group; (b) this strategy is very useful to stereostructural analysis of polyene alcohol compound in natural products chemistry.
10. The plausible intermediate can be visualized as follows: