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Cross-metathesis approach to a (2*E*,4*E*)-dienoic acid intermediate for the synthesis of elaiolide

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Abstract—A (2*E*,4*E*)-7-hydroxy-2,4-dienoic acid, previously employed as a key intermediate for the total synthesis of the macrodiolide antibiotic elaiolide, was prepared stereoselectively and concisely from (*S*)-2-methyl-3-trityloxypropanal by a three-step sequence consisting of Brown's asymmetric crotylboration, olefin cross-metathesis, and alkaline treatment. Ethyl 3-pivaloyloxy-4-pentenoate was used as a masked dienoate in the cross-metathesis step.

Elaiophylin (**1**), a glycosidic polyketide featuring a 16-membered macrodiolide core structure, was first isolated from the culture broth of *Streptomyces melanosporus* by Arcamone et al. as a potent antibiotic against Gram-positive bacteria (Fig. 1).[1] After the discovery, **1** was reisolated from other species of *Streptomyces* by several groups as azalomycin B,[2] antibiotic 255-E,[3] salbomycin,[4] and gopalamicin.[5] In addition to the antibiotic activity, **1** is also known to possess a wide range of bioactivities such as cell cycle inhibitory and apoptosis inducing activities,[6] immunosuppressive activity,[7] and plant growth inhibitory activity.[8] The structure of **1**, including its absolute stereochemistry, was determined on the basis of its X-ray crystallographic analysis[9] following the spectroscopic assignment of its gross structure.[10] The attractive biological activities as well as the complicated C_2-symmetric architecture of **1** have stimulated considerable interest in its synthesis,[11] which culminated in the total synthesis of **1** by the Kinoshita group in 1986 after the achievement of the synthesis of 11,11′-di-*O*-methylelaiolide (**2**) by Seebach and co-workers in the preceding year.[12,13] Synthesis of elaiolide (**3**), the aglycon of **1**, was also reported by Evans et al.[14] and Paterson et al.[15] Except for the Paterson synthesis, which utilized a Stille cyclodimerization reaction for the installation of the macrodiolide core, the other three syntheses employed the double Yamaguchi esterification

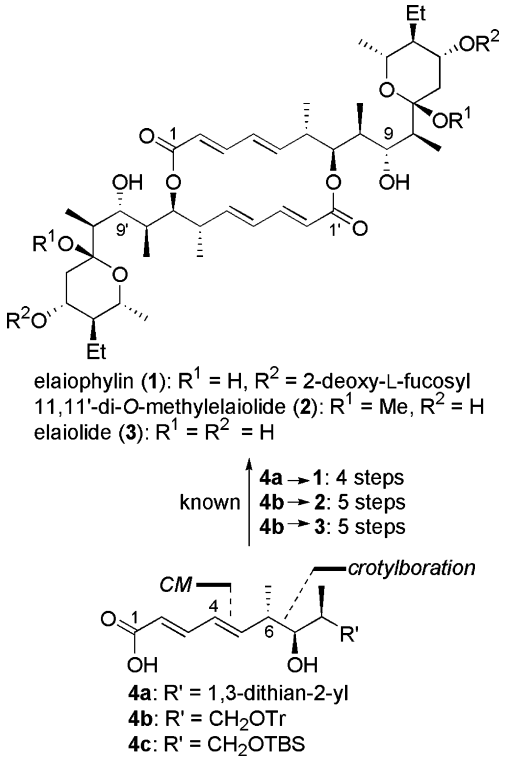

Figure 1. Structures of elaiophylin and related compounds, and the retrosynthetic analysis of their cyclodimerization precursors.

Keywords: Elaiolide; Cross-metathesis; Enantioselective synthesis; Antibiotic; 2,4-Alkadienoic acid.
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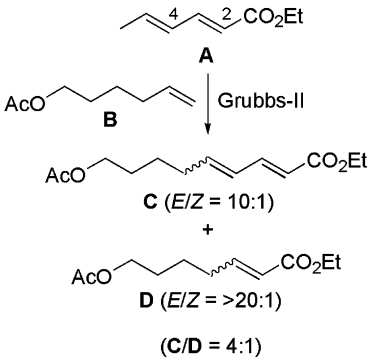


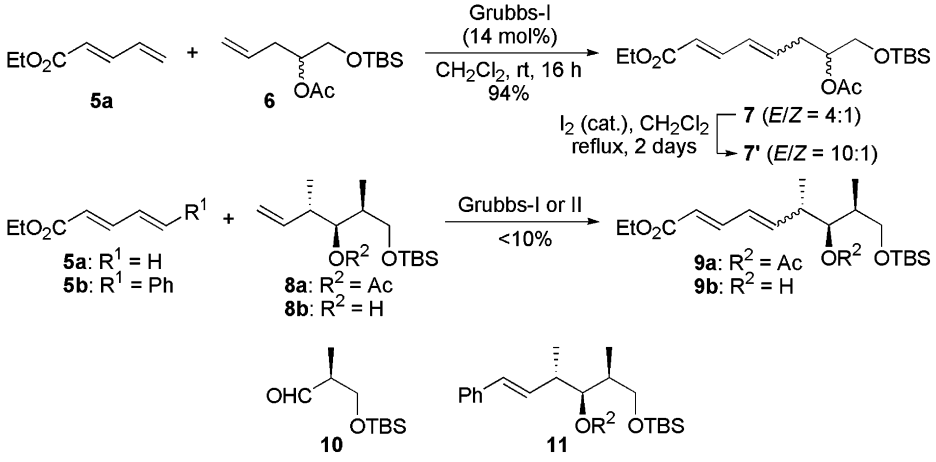
Figure 2. A precedent for the cross-metathesis reaction of an *E*,*E*-dienoate with a terminal monoene by Grubbs et al.

of hydroxy acid **4a** or **4b** for the 16-membered ring formation, and the resulting macrocyclic intermediates were successfully converted into **1**, **2**, or **3** in short-step sequences by taking advantage of their C_2-symmetric nature. The dimerization precursor **4a**, in turn, was obtained from D-glucose through a considerably long reaction sequence,[12] while the other precursor **4b** was prepared from ethyl (*S*)-3-hydroxy-2-methylpropanoate or methacrolein in 13 or 9 steps, respectively, involving a chiral oxazolidinone-induced asymmetric aldol reaction as a key step.[13,14] Herein, we report an efficient approach to the monomeric *seco*-acid (**4b** or its TBS-protected congener **4c**) by means of olefin cross-metathesis for the construction of the trans C4–C5 double bond and asymmetric crotylboration for the C6–C7 bond formation.

Although cross-metathesis reactions of two monoenes have been well-studied and applied successfully to total syntheses of many natural products, the cross-metathesis of a diene with a monoene has not been investigated so much.[16] Especially, investigation of the cross-metathesis between 2,4-dienoates and monoenes to form 2,4-alkadienoates has only limited precedents. Recently, Grubbs et al. reported that the cross-metathesis reaction of ethyl (2*E*,4*E*)-2,4-hexadienoate (**A**) with terminal olefin **B** in the presence of the first-generation Grubbs catalyst (Grubbs-I) gave only the homocoupling product of **B**, while on exposure to the second-generation Grubbs catalyst (Grubbs-II) afforded a 4:1 mixture of cross-metathesis products, **C** and **D**, resulting from reactions at either the C4–C5 or the C2–C3 double bonds of dienoate **A** (Fig. 2).[17] Inspired by this precedent and some related studies,[18] we first examined the feasibility of direct installation of the (2*E*,4*E*)-2,4-alkadienoate system in *seco*-acid **4** using the cross-metathesis reaction between ethyl 2,4-pentadienoate (**5a**) and terminal olefin **6** as a model case (Scheme 1).

As shown in Scheme 1, the cross-metathesis reaction of **5a** and **6**[19] proceeded smoothly at room temperature in the presence of 14 mol % Grubbs-I catalyst, giving 94% yield of the desired C4–C5 metathesis product **7** as a 4:1 *E*/*Z* mixture,[20] and the geometrical ratio could be readily improved to 10:1 by equilibration with a catalytic amount of I_2 in refluxing CH_2Cl_2. With these promising preliminary results in hand, we set about the cross-metathesis of **5a** with **8a**, which was obtainable from **10**[21] using Brown's asymmetric crotylboration followed by acetylation of the resulting homoallylic alcohol **8b**.[22] Despite scrutiny of various reaction conditions [type and amount of Grubbs' catalysts (1st or 2nd, 10–30 mol %), amount of **5a** (3–6 equiv), solvent (CH_2Cl_2, toluene), temperature (25–100 °C), use of Lewis acid catalyst ($Ti(OiPr)_4$),[23] and microwave irradiation[24]], all reaction conditions tried resulted only in miserably low yields of the desirable product **9a** (<10% yield, as *E*/*Z* mixtures). Similar attempts using **8b** to obtain **9b** were also unsuccessful, and alteration of the dienoate component from **5a** to **5b** did not bring any fruitful outcome, giving mainly a low yield of **11** generated through an undesirable metathesis pathway.

In order to circumvent this difficulty, we next tried the use of non-conjugated olefin **12** as a masked dienoate (Scheme 2).[25] After several examinations of reaction conditions, we found that the cross-metathesis of **8b** with **12** proceeded in the presence of Grubbs-II catalyst (15–20 mol %) under microwave irradiation conditions,[24] giving a mixture containing **13** as the major constituent in about 60% yield.[26] Subjection of the mixture



Scheme 1.