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Tetrahedron Letters

Tetrahedron Letters 48 (2007) 3163–3166

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

Akira Morita and Shigefumi Kuwahara*

*Laboratory of Applied Bioorganic Chemistry, Graduate School of Agricultural Science, Tohoku University, Tsutsumidori-Amamiyamachi, Aoba-ku, Sendai 981-8555, Japan*

Received 8 February 2007; revised 7 March 2007; accepted 9 March 2007
Available online 12 March 2007

**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

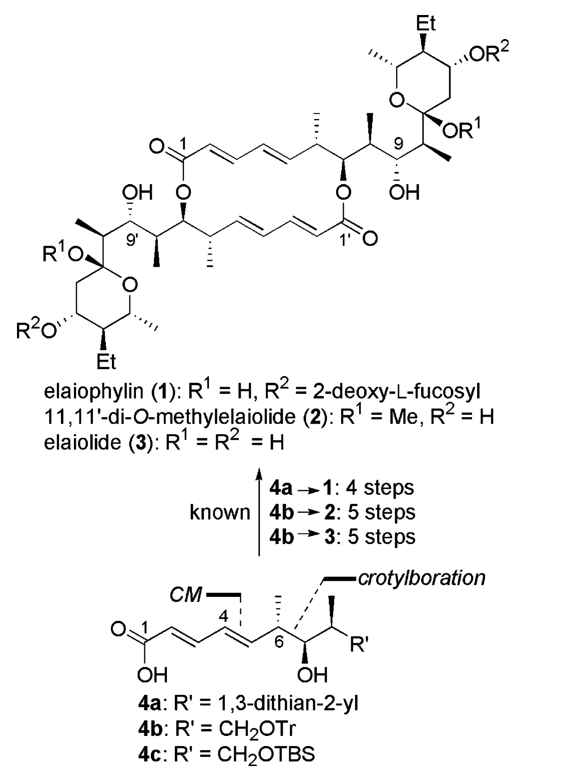


**Figure 1.** Structures of elaiophylin and related compounds, and the retrosynthetic analysis of their cyclodimerization precursors.

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

* Corresponding author. Tel./fax: +81 22 717 8783; e-mail: skuwahar@biochem.tohoku.ac.jp

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doi:10.1016/j.tetlet.2007.03.055

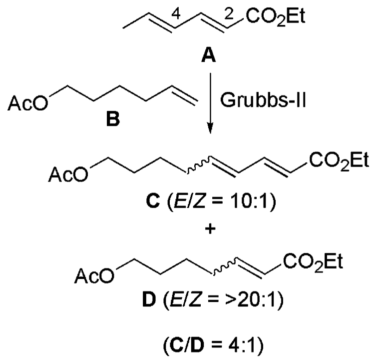


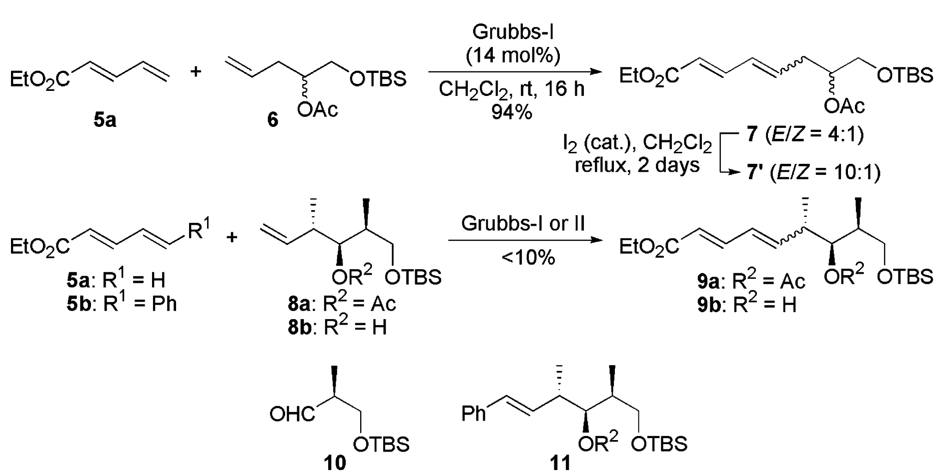

**Figure 2.** A precedent for the cross-metathesis reaction of an *E*,*E*-dienoate with a terminal monoene by Grubbs et al.

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.

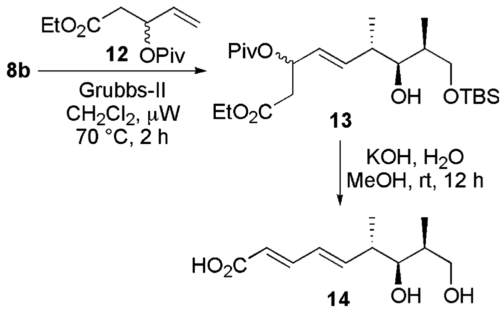
Although cross-metathesis reactions of two monoenes have been well-studied and applied successfully to total syntheses of many natural products, the cross-metathesis of a diene with a monoene has not been investigated so much.[16] Especially, investigation of the cross-metathesis between 2,4-dienoates 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 ($Ti(O\textit{i}Pr)_4$),[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.

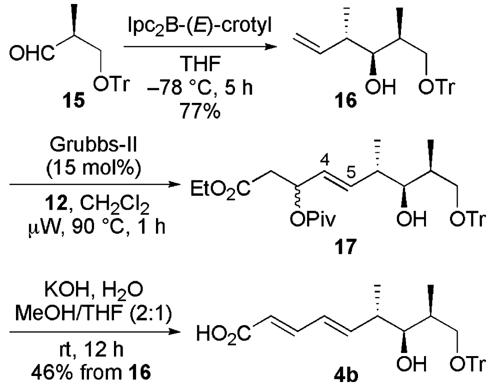
In order to circumvent this difficulty, we next tried the use of non-conjugated olefin **12** as a masked dienoate (Scheme 2).[25] After several examinations of reaction conditions, we found that the cross-metathesis of **8b** with **12** proceeded in the presence of Grubbs-II catalyst (15–20 mol %) 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.**




**Scheme 2.**




**Scheme 3.**

to aqueous KOH in methanol brought about β-elimination of the pivaloyloxy group and concomitant hydrolysis of the ethyl ester moiety as expected, but the TBS-protecting group was also removed under the basic conditions to afford dihydroxy acid **14**.[27] This result made us seek another protecting group compatible with the basic conditions.

We eventually selected the trityl protecting group, which would enable us to lead to the known hydroxy acid **4b** (Scheme 3). Readily available aldehyde **15**[28] was exposed to Brown's asymmetric crotylboration conditions to give **16** (77% isolated yield) and its diastereomer (8% isolated yield) after chromatographic purification.[29] The desired olefin **16** was then allowed to react with **12** in the presence of Grubbs-II catalyst (15 mol %) under irradiation of microwave at 90 °C for 1 h (30 min × 2) to furnish **17**; the geometry of the newly formed C4–C5 double bond was revealed to be homogeneous and exclusively *E* from the 4-H/5-H coupling constant (15.1 Hz). Metathesis product **17** was then treated with aqueous KOH in MeOH/THF to give smoothly target molecule **4b** in 46% yield from **16**.[30] Hydroxy acid **4b** was previously converted into elaiolide (**3**) in five steps by Evans et al.,[14] and a dimeric dialdehyde obtainable from **4b** via a three-step sequence[13,14] was successfully transformed into elaiophylin (**1**) in two steps by Kinoshita et al.[12]

In conclusion, we accomplished the concise synthesis of (2*E*,4*E*)-7-hydroxy-2,4-dienoic acid **4b**, a key intermediate for the synthesis of **2** and **3**, from readily available aldehyde **15** using a three-step sequence consisting of Brown's asymmetric crotylboration, olefin cross-metathesis, and hydrolysis accompanied by concurrent elimination.

## Acknowledgments

We thank Ms. Yamada (Tohoku University) for measuring NMR and MS spectra. This work was supported, in part, by a Grant-in-Aid for Scientific Research (B) from the Ministry of Education, Culture, Sports, Science and Technology of Japan (No. 16380075).

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19. Compound **6** was readily obtained from the bis-TBS ether of (*Z*)-2-butene-1,4-diol in three steps ($O_3$, $CH_2Cl_2$, −78 °C, then $Me_2S$; $CH_2{=}CHCH_2MgBr$, ether, 0 °C; $Ac_2O$, Py, 20 °C).
20. Compound (*E*)-**7**: IR (film) $\nu_{max}$ 1741 (s), 1717 (s), 1645 (w); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.05 (6H, s), 0.89 (9H, s), 1.30 (3H, t, $J = 7.1$ Hz), 2.04 (3H, s), 2.44 (1H, dt, $J = 14.4$, 7.4 Hz), 2.54 (1H, dt, $J = 14.4$, 6.8 Hz), 3.62 (1H, dd, $J = 10.7$, 4.9 Hz) 3.65 (1H, dd, $J = 10.7$, 4.9 Hz), 4.20 (2H, q, $J = 7.1$ Hz), 4.92–4.97 (1H, m), 5.81 (1H, d, $J = 15.3$ Hz), 6.05 (1H, dt, $J = 6.9$, 15.3 Hz), 6.23 (1H, dd, $J = 11.2$, 15.3 Hz), 7.24 (1H, dd, $J = 11.2$, 15.3 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ −5.5, 14.3, 18.2, 21.1, 25.7, 34.1, 60.2, 63.5, 73.2, 120.3, 131.1, 138.2, 144.2, 167.0, 170.4; HRMS (FAB): *m*/*z* calcd for $C_{18}H_{33}O_5Si$, 357.2098; found, 357.2096 ($[M+H]^+$).
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25. Compound **12** was obtained from ethyl 3-hydroxy-4-pentenoate in 83% yield by treatment with PivCl in Py in the presence of a catalytic amount of DMAP. For the preparation of the hydroxy ester, see: Zibuck, R.; Streiber, J. M. *J. Org. Chem.* **1989**, *54*, 4717–4719.
26. When a mixture of **8b**, **12**, and Grubbs-II catalyst (15 mol %) was refluxed in $CH_2Cl_2$ without microwave irradiation, the metathesis reaction was very sluggish, giving a mixture containing starting material **8b** and the desired product **13** in a ratio of ca. 1:1 even after 2 days (as judged by the $^1$H NMR analysis of the crude reaction mixture). The double bond geometry of **13** could not be determined by NMR at this stage because of the presence of overlapping signals due to the olefinic protons of the contaminating homocoupling product of **12**.
27. Although the exact chemical yield of dihydroxy acid **14** from **13** could not be determined due to the high solubility of **14** in water, TLC monitoring of the reaction indicated that **14** was produced almost quantitatively. The *E*,*E*-geometry of **14** was assigned from its $^1$H NMR coupling constants (2-H/3-H, 15.1 Hz; 4-H/5-H, 15.1 Hz).
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29. Compound **16**: $[\alpha]_D^{22}$ −3.2 (*c* 0.96, $CHCl_3$); IR (film) $\nu_{max}$ 3507 (br, m), 3058 (m), 1597 (w), 1490 (m), 1448 (s); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.93 (3H, d, $J = 7.0$ Hz), 1.02 (3H, d, $J = 7.5$ Hz), 1.83–1.91 (1H, m), 2.17–2.25 (1H, m), 2.27 (1H, d, $J = 2.5$ Hz, OH), 3.11 (1H, dd, $J = 5.0$, 8.9 Hz), 3.26 (1H, dd, $J = 5.8$, 8.9 Hz), 3.44–3.48 (1H, m), 5.04 (1H, d, $J = 17.1$ Hz), 5.05 (1H, d, $J = 10.3$ Hz), 5.77 (1H, ddd, $J = 8.3$, 10.3, 17.1 Hz), 7.22 (3H, t, $J = 7.4$ Hz), 7.27 (6H, t, $J = 7.4$ Hz), 7.44 (6H, d, $J = 7.4$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 10.3, 16.8, 35.4, 41.6, 67.4, 76.2, 86.7, 115.4, 126.9, 127.8, 128.6, 141.7, 144.0; HRMS (EI) *m*/*z*: calcd for $C_{27}H_{30}O_2$, 386.2246; found, 386.2251 ($M^+$).
30. *Preparation of* **4b**: To a stirred solution of **16** (66.5 mg, 0.172 mmol) and **12** (112 mg, 0.491 mmol) in $CH_2Cl_2$ (1.3 mL) in a test tube was added Grubbs-II catalyst (14.7 mg, 17.3 μmol) under a nitrogen atmosphere. The reaction vessel was capped with a septum and inserted into the cavity of a Discover Microwave System apparatus (from CEM) and irradiated at 300 W for 30 min (internal temperature 90 °C, controlled and monitored with the standard infrared temperature control system for the Discover System). After cooling to room temperature, **12** (59.2 mg, 0.259 mmol), Grubbs-II catalyst (8.0 mg, 9.4 μmol) and $CH_2Cl_2$ (0.5 mL) were added again, and the mixture was re-irradiated for additional 30 min under the same irradiation conditions. The reaction mixture was filtered through Florisil and the filtrate was concentrated in vacuo. The residue was chromatographed over $SiO_2$ (hexane/EtOAc, 10:1) to give 153 mg of **17** as a yellow oil, which was then taken up in MeOH/THF (2:1, 4.5 mL). To the solution was added dropwise aqueous KOH (1.1 M, 4.5 mL, 5.0 mmol) at room temperature. The mixture was stirred overnight, and then concentrated in vacuo. The residue was diluted with water, acidified to pH 3 with 0.5 M aqueous HCl at 0 °C, and extracted EtOAc. The extract was dried ($MgSO_4$) and concentrated in vacuo. The residue was chromatographed over $SiO_2$ [hexane/EtOAc (3:1) containing a trace amount of AcOH] to give 36.3 mg (46%) of **4b** as a white solid. $[\alpha]_D^{22}$ −14.3 (*c* 1.57, $CHCl_3$); IR (film) $\nu_{max}$ 3500–2600 (br), 3058 (m), 3024 (m), 1686 (s), 1637 (m), 1616 (w), 1448 (m), 1274 (m), 1002 (m); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 0.97 (3H, d, $J = 7.0$ Hz), 1.06 (3H, d, $J = 7.3$ Hz), 1.81–1.88 (1H, m), 2.29–2.38 (1H, m), 3.12 (1H, dd, $J = 3.8$, 9.0 Hz), 3.26 (1H, dd, $J = 5.3$, 9.0 Hz), 3.55 (1H, dd, $J = 3.0$, 8.0 Hz), 5.77 (1H, d, $J = 15.0$ Hz), 6.12 (1H, dd, $J = 10.3$, 15.1 Hz), 6.17 (1H, dd, $J = 7.8$, 15.1 Hz), 7.24 (3H, t, $J = 7.3$ Hz), 7.30 (6H, t, $J = 7.3$ Hz), 7.32 (1H, dd, $J = 15.0$, 10.3 Hz), 7.43 (6H, d, $J = 7.3$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 10.7, 16.8, 35.7, 40.7, 67.3, 77.0, 86.8, 119.0, 127.1, 127.9, 128.4, 128.6, 143.8, 147.1, 148.2, 172.3; HRMS (FAB): *m*/*z* calcd for $C_{30}H_{32}O_4Na$, 479.2198; found, 479.2200 ($[M+Na]^+$).