Tetrahedron 67 (2011) 9622–9626

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Grubbs carbene complex-catalyzed cleavage of allyl *vic*-diols to aldehydes with a co-oxidant: application to the selective cleavage of huge marine molecules

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ARTICLE INFO

Article history:
Received 21 July 2011
Received in revised form 1 September 2011
Accepted 2 September 2011
Available online 8 September 2011

Keywords:
Grubbs carbene complex
Catalytic reaction
Marine huge molecule
Degradation reaction

ABSTRACT

An oxidative cleavage of allyl *vic*-diols to aldehydes catalyzed by a Grubbs carbene complex using a co-oxidant has been established for the first time, with good yields. The utility of this selective cleavage reaction was demonstrated through the use of two huge marine molecules, symbiodinolide and *N*-*p*-BrBz palytoxin.

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1. Introduction

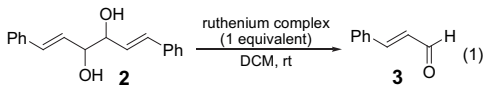
Transition metal–carbene complexes are well-recognized as intermediates in homogeneous catalytic olefin metathesis.[1] Among these complexes, molybdenum–alkylidene complexes (Schrock catalyst)[2] and ruthenium–alkylidene complexes (Grubbs catalyst)[3] have created new possibilities in organic synthesis for constructing C–C double bonds.[4] Several complexes are commercially available, and, in particular, the second-generation Grubbs catalyst (Grubbs II catalyst) has become an important tool for the synthesis of natural products because of its high tolerance toward functional groups, high stability, and high activity toward olefins.[5] Grubbs II catalyst is often used in ring-closing, ring-opening, and cross-metatheses of olefins.[5] Interestingly, however, Grubbs complexes are rarely used as catalysts for other transformations of olefins.

Very recently, we reported the Grubbs II complex-mediated specific oxidation of allyl *vic*-diols to the corresponding aldehydes.[6] This oxidative *vic*-diol cleavage protocol is highly useful because only *vic*-diols with an allylalcohol moiety are oxidized, while dialkyl *vic*-diols are not consumed during the reaction. The major drawback of this reaction is that a stoichiometric amount of expensive Grubbs II complex must be used to achieve high efficiency.

We report here the Grubbs II complex-catalyzed specific oxidation of allyl *vic*-diols with a co-oxidant and the application of this transformation to the degradation of huge marine molecules, such as 'super-carbon-chain compounds (SCC)',[7] symbiodinolide, and *N*-*p*-BrBz-substituted palytoxin.

2. Results and discussion

We previously demonstrated that the Grubbs II complex **1** showed high activity for the stoichiometric oxidation of 1,6-diphenyl-1,5-hexadiene-3,4-diol (**2**) to cinnamaldehyde (**3**) (94% yield) (Eq. 1).[6a] The activities of other ruthenium complexes such as $RuCl_3$, RuO_2, $RuCl_2(PPh_3)_3$, and Grubbs I complexes in the reaction of **2** were examined using a stoichiometric amount of the complex (Eq. 1). In these cases, the yields decreased to 0–64%. Therefore, Grubbs II complex was considered to be a suitable catalyst for this reaction.



As a working hypothesis for oxidative cleavage of the C–C bond at an allyl *vic*-moiety in a catalytic manner, we considered the reaction pathway. The initial step involves ligand-exchange between Grubbs II complex and the allyl *vic*-alcohol. In the second step, the diol is oxidized to the corresponding aldehydes and the Ru complex

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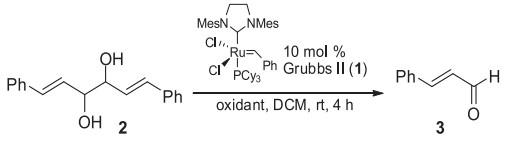
0040-4020/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2011.09.002

is reduced to Ru(II) species. Oxidation of Ru(II) species with an oxidant to regenerates Ru(IV) species.

We chose diallyl *vic*-diol **2** as a test substrate for the screening of co-oxidants in the Grubbs II complex-catalyzed oxidation. The reaction of **2** with a co-oxidant was carried out in the presence of 10 mol % Grubbs II catalyst in dichloromethane at room temperature. The results are shown in Table 1. The reaction in the absence of a terminal oxidant afforded **3** in 6% yield (entry 1). A combination of Grubbs II and Chloramine-T or NCS showed low catalytic activity (entries 2 and 3). The use of O_2, H_2O_2, or TBHP was not effective (entries 4–6). Between two amine oxides screened (entries 7–8), NMO functioned as a good co-oxidant and **3** was obtained in 73% yield (entry 8). The oxidation using NaClO led to **3** in high yield (90%) (entry 9).

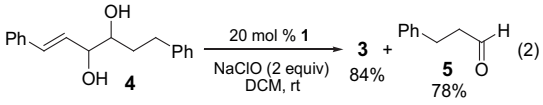
Table 1
Screening of oxidants for the catalytic cleavage of allyl *vic*-alcohol **2**[a]



Entry	Oxidant	Yield of **3**[b]
1	None	6%
2	Chloramine-T	10%
3	NCS	25%
4	O_2	29%
5	H_2O_2	17%
6	TBHP	4%
7	Pyridine-*N*-oxide	8%
8	NMO	73%
9	NaClO	90%

[a] Reaction conditions: Grubbs II complex **1** (10 mol %), **2** (0.02 mmol), oxidant (2 equiv), DCM (1 mL), rt.
[b] Isolated yield based on **2**.

Diallyl *vic*-diol substructures are not essential to achieve high reactivity, since monoallyl *vic*-diol **4** was also oxidized under similar reaction conditions except for the catalyst loading (20 mol %) to give the corresponding aldehydes **3** and **5** in respective yields of 84% and 78% (Eq. 2). On the other hand, dialkyl *vic*-diol was completely inactive under these reaction conditions, although it had been reported as a catalyzed oxidative cleavage to aldehydes with O_2 by $Ru(PPh_3)Cl_2$.[8] These results indicate that at least one allyl *vic*-diol substructure is essential for this Grubbs II complex-catalyzed oxidative cleavage reaction. We envisioned that the present catalytic cleavage of allyl *vic*-diols using NaClO as a co-oxidant could be used for the selective degradation of natural products containing multiple *vic*-diol moieties.



Two huge marine molecules, symbiodinolide, and *N*-*p*-BrBz palytoxin, contain allyl *vic*-diol and multiple *vic*-diol moieties and were used as substrates to validate the practicability of the Grubbs II complex-catalyzed oxidation of allyl *vic*-diols using NaClO. A *seco* ester[9] of symbiodinolide (**6**) was first obtained by methanolysis, and the catalytic cleavage of **6** was then performed in the presence of commercially available Grubbs II complex **1** (10 mol %) with NaClO (7 equiv) in MeOH at room temperature for 4 h. The corresponding αβ,γδ-unsaturated aldehyde **7** (C1–C13 fragment) and α,β-unsaturated aldehyde **8** (C14–C25′ fragment) were obtained in respective yields of 86% and 76% due to the selective cleavage of (*E*)-diallyl *vic*-diol (Scheme 1).

The stereochemistries at C5, C6, and C7 of the C1–C13 fragment were assigned on the basis of the Universal NMR Database approach.[10] The chemical shifts of H5 and H7 were observed at δ 3.97 ppm in D_2O, which indicated the presence of a plane of symmetry for fragment **7**. Two contiguous $^3J_{H,H}$ constants ($^3J_{5,6}=^3J_{6,7}=4.5$ Hz) are identical and fairly small (as a general trend, a *syn*-diol gives a smaller $^3J_{HH}$ constant than the corresponding *anti*-diol). These results are consistent with the universal NMR database of 1,2,3-triol 1a (ααα), and therefore the relative stereochemistries at C5, C6 and C7 could be proposed as 5*R**, 6*R**, and 7*S** (Scheme 1).

In addition, a (*Z*)-monoallyl *anti*-diol substructure in *N*-*p*-BrBz palytoxin (**9**) was selectively cleaved in the presence of 50 mol % Grubbs II catalyst and NaClO (6 equiv) in MeOH at room temperature (Fig. 1), and two degradation products, *N*-*p*-bromobenzoyl aldehyde **10**[11] and α,β-unsaturated aldehyde **11** (Cf–C100 fragment), were obtained in Fig. 2. These results indicate that Grubbs II complex-catalyzed selective cleavage using NaClO might be suitable for the conversion of both *E*- and *Z*-allyl *vic*-diols to aldehydes in natural products, especially large polyol compounds for stereostructural analysis, since multiple *vic*-diol moieties could not be cleaved during the reaction.

Another example of a diol cleavage reaction was also demonstrated. Pseurotin A is a natural product of a fungal metabolite with a diallyl diol moiety, and it possesses neuritogenic activity in PC12 phaechromocytoma cells.[12] Pseurotin A was subjected to the catalytic diol cleavage conditions (Grubbs II catalyst 0.1 equiv—NMO 20 equiv in $MeOH/CH_2Cl_2$; rt 4 h) and gave the expected aldehyde **12** in >90% yield without any side products (Scheme 2).

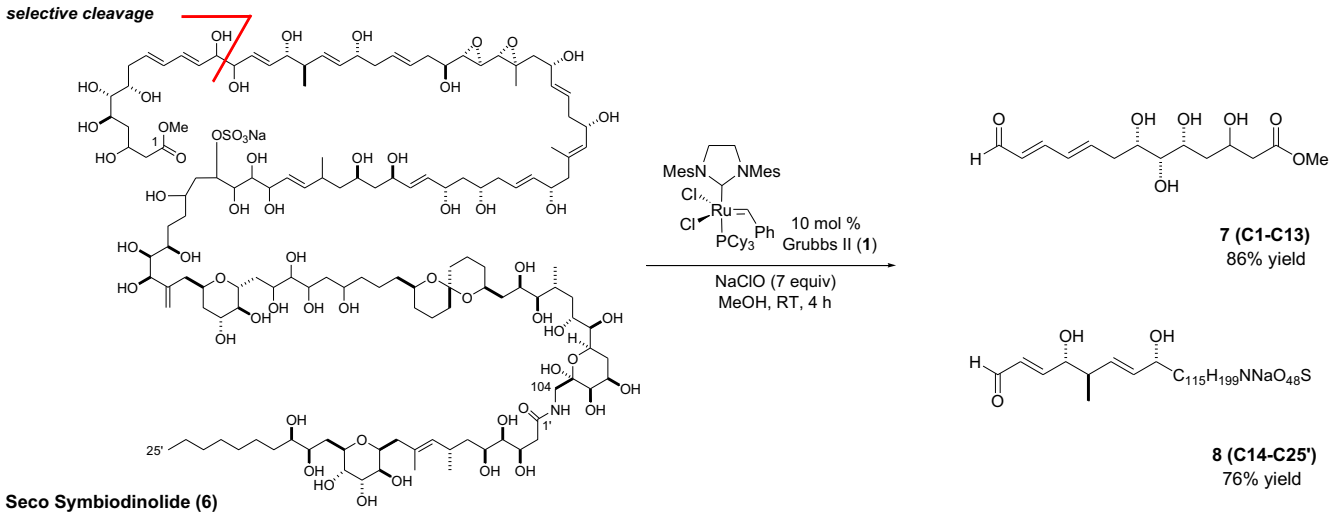
For the present catalytic cleavage of allyl *vic*-diols using NaClO, we propose the reaction pathway shown in Scheme 3. Ru(II) species **C** was oxidized by NaClO (or some other co-oxidant) to give the oxoruthenium Ru(IV) species **A**. Ligand-exchange occurs between **A** and allyl *vic*-diol **B**, and the diol is then oxidized to the corresponding aldehydes and water. The Ru complex is reduced to Ru(II) species **C**, thereby completing the catalytic cycle.

In summary, we have developed a new efficient method for the Grubbs II complex-catalyzed oxidative cleavage of *E*- and *Z*-allyl *vic*-diol using NaClO or some other co-oxidant under very mild reaction conditions. We demonstrated the utility of this catalytic cleavage for the first time using two huge marine molecules, symbiodinolide and *N*-*p*-BrBz palytoxin. This reaction is highly useful for stereostructural analysis in natural products chemistry, especially in polyene alcohol compounds, since this cleavage reaction gives only simple products; i.e., while *vic*-diols with an allylalcohol moiety are oxidized, dialkyl *vic*-diol (e.g., triol or tetraol) in the same molecule is not.

3. Experimental

3.1. General information

^1H NMR spectra were recorded on a JEOL JNM-ECA800 spectrometer. Chemical shifts are expressed in parts per million relative to residual chloroform (δ_H 7.26 for ^1H), or CD_3OD (δ_H 3.30 for ^1H). Coupling constants are reported in hertz (Hz) and the peak multiplicity is listed as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet. Peak assignments were made with the aid of the COSY method. High-resolution mass spectra (HR-ESIMS) were obtained on a PE Biosystems QSTAR mass spectrometer. Column chromatography was performed with Wako Pure Chemical Silica-gel (Wakogel® C-300) and Nacalai Tesque Cosmosil $75C_{18}$-OPN. Merck silica-gel 60 F_{254} plates were used for thin-layer chromatography (TLC).



Scheme 1. Selective cleavage of *seco*-symbiodinolide.

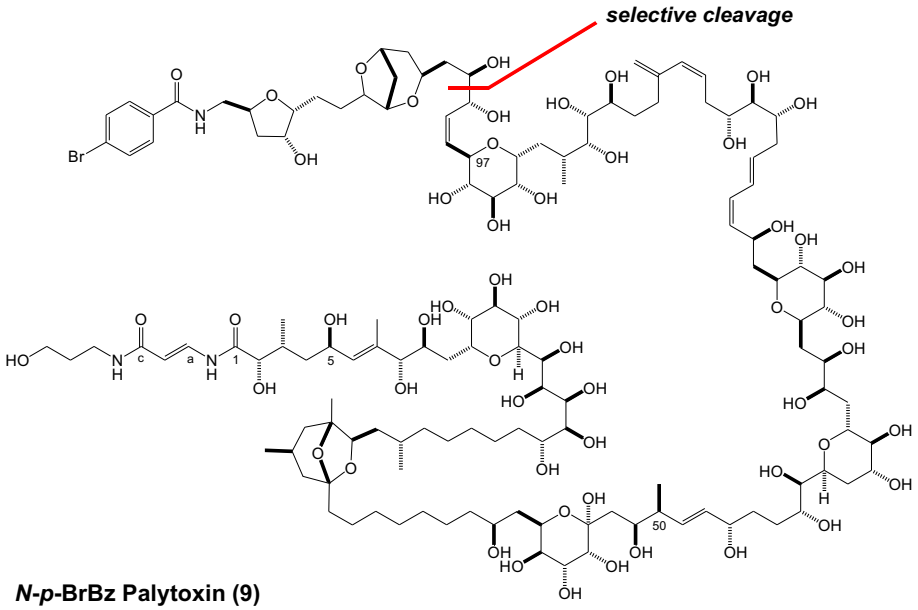


Fig. 1. Structure of *N*-*p*-BrBz palytoxin.

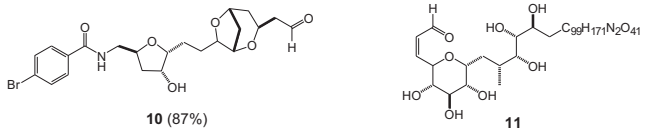
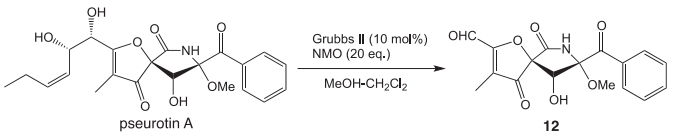
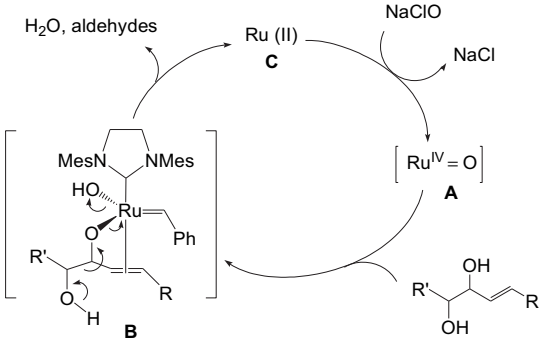


Fig. 2. Structure of degradation products of *N*-*p*-BrBz palytoxin.



Scheme 2. Selective cleavage of pseurotin A.



Scheme 3. Proposed reaction pathway for catalytic cleavage of allyl *vic*-diols using NaClO.

3.2. Synthesis of 1,6-diphenyl-1,5-hexadiene-3,4-diol (2)

Propionitrile (20 mmol) was added to TiI_4 (11.1 g, 20 mmol) at ambient temperature under an argon atmosphere. The solution was stirred for 10 min, and to it was added a propionitrile (20 mL) solution of cinnamaldehyde **3** (1.3 g, 9.8 mmol) at −78 °C. After being stirred at −78 °C to −20 °C, the reaction was quenched with satd aqueous $NaHCO_3$, 10% aqueous $NaHSO_3$, and triethylamine. The whole mixture was filtered through a Celite pad and extracted with

ethyl acetate (50 mL×3). The combined organic extracts were dried over anhydrous Na_2SO_4, and evaporated in vacuo. The residue was subjected to column chromatography on silica-gel (CH_2Cl_2/EtOAc=2/1 as an eluent) to give 1,6-diphenyl-1,5-hexadiene-3,4-diol **2** (1.1 g, 83%) as a white solid. ^{1}H NMR ($CDCl_3$): δ 2.45 (br s, 2H), 4.26 (m, 2H), 6.25 (dd, J=5.5, 15.8 Hz, 2H), 6.71 (d, J=15.8 Hz), 7.23 (m, 2H), 7.29 (t, J=7.6 Hz, 4H), 7.36 (J=7.6 Hz, 4H). HRMS (ESI) calcd for $[M+Na]^+$ ($C_{18}H_{18}O_2Na$) m/z 289.1204. Found 289.1210.

3.3. Synthesis of 1,6-diphenyl-1-hexene-3, 4-diol (4)

1,6-Diphenyl-1,5-hexadiene-3,4-diol **2** (5.3 mg, 0.02 mmol) was dissolved in MeOH (1.0 mL), and 0.4 mg of Rh/C (wt 5%) was added. The solution was stirred under a hydrogen atmosphere (balloon) for 1 h at room temperature. The catalyst was removed through a filter (Minisart RC 4, 0.45 μm, Goettingen, Germany), and the filtrate was evaporated and purified by HPLC [Develosil ODS-HG-5 (Ø 10×250 mm), 60% aqueous MeCN, flow rate 2 mL/min, RI detection] to give monoallyl *vic*-diol **4** (3.2 mg, 60%, t_R=15.93–16.77 min) as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.71 (dddd, J=5.2, 9.3, 9.8, 13.8 Hz, 1H), 1.86 (dddd, J=3.4, 7.2, 10.3, 13.8 Hz, 1H), 2.66 (ddd, J=7.2, 9.8, 13.6 Hz, 1H), 2.84 (ddd, J=5.2, 10.3, 13.6 Hz, 1H), 3.53 (ddd, J=3.4, 5.7, 9.3 Hz, 1H), 4.09 (dd, J=5.7, 6.9 Hz, 1H), 6.26 (dd, J=6.8, 15.8 Hz, 1H), 6.62 (d, J=15.8 Hz, 1H), 7.12 (t, J=7.3 Hz, 1H), 7.17–7.23 (m, 5H), 7.28 (t, J=7.9 Hz, 2H), 7.38 (J=7.9 Hz, 2H). HRMS (ESI) calcd for $[M+Na]^+$ ($C_{18}H_{20}O_2Na$) m/z 291.1357. Found 291.1361.

3.4. Stoichiometric oxidation of 1,6-diphenyl-1,5-hexadiene-3,4-diol (2) to cinnamaldehyde (3)

A solution of 1,6-diphenyl-1,5-hexadiene-3,4-diol **2** (5.3 mg, 0.02 mmol) in anhydrous MeOH (0.8 mL) was degassed three times and then placed under an argon atmosphere. To the above stirred solution was added the ruthenium complex (0.02 mmol) in 0.2 mL of DCM, and the mixture was stirred for 4 h at room temperature in the dark. The reaction mixture was concentrated in vacuo, and the residue was subjected to column chromatography on silica-gel (eluent; toluene) to give *trans*-cinnamaldehyde **3**: 3.4 mg (64% yield by $RuCl_2(PPh_3)_3$, 1.8 mg (34% yield by Grubbs I catalyst), trace ($RuCl_3$), NR (RuO_2). ^{1}H NMR ($CDCL_3$) δ 6.73 (dd, J=7.6, 15.8 Hz, 1H), 7.44 (m, 3H), 7.49 (d, J=15.8 Hz, 1H), 7.57 (m, 2H), 9.71 (d, J=7.6 Hz, 1H). HR-ESIMS calcd for $[M+H]^+$ (C_9H_9O) m/z 133.0656. Found 133.0653.

3.5. Typical procedure for screening of oxidants for the catalytic cleavage of allyl *vic*-alcohol (2)

The solution of diallyl *vic*-diol **2** (5.3 mg, 0.02 mmol) in dichloromethane (0.9 mL) was degassed and then placed under an argon atmosphere. To the above stirred solution was added the second-generation catalyst (20 mM in dichloromethane, 0.1 mL, 0.002 mmol) and NaClO (16 mL, 0.04 mmol), and the mixture was stirred for 4 h at room temperature in the dark. The reaction was quenched with satd aqueous Na_2SO_3. The mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated in vacuo. The residue was subjected to column chromatography on silica-gel (eluent; toluene) to give *trans*-cinnamaldehyde **3** (4.8 mg, 90%) as a yellow liquid.

3.6. Catalytic cleavage of monoallyl *vic*-alcohol (4) to benzenepropenal (3) and benzenepropanal (5)

The solution of monoallyl *vic*-diol **4** (5.4 mg, 0.02 mmol) in dichloromethane (0.9 mL) was degassed and then placed under an argon atmosphere. To the above stirred solution was added the second-generation catalyst (40 mM in dichloromethane, 0.1 mL, 0.004 mmol) and NaClO (16 mL, 0.04 mmol), and the mixture was stirred for 4 h at room temperature in the dark. The reaction was quenched with satd aqueous Na_2SO_3. The mixture was extracted with CH_2Cl_2 (10 mL×3). The combined organic extracts were dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was subjected to column chromatography on silica-gel (eluent; toluene) to give benzenepropenal **3** (2.2 mg, 84%) and benzenepropanal **5** (2.1 mg, 78%); ^{1}H NMR ($CDCl_3$) δ 2.79 (m, 2H), 2.96 (m, 2H), 7.19 (m, 3H), 7.29 (m, 2H), 9.81 (br s, 1H). HR-ESIMS calcd for $[M+H]^+$ ($C_9H_{11}O$) m/z 135.081. Found 135.086.

3.7. Methanolysis of symbiodinolide

To a stirred solution of symbiodinolide (4.4 mg, 1.5 μmol) in MeOH (3.6 mL) was added Et_3N (1.1 mL). After the reaction mixture was stirred for 46 h at room temperature, it was concentrated under reduced pressure to give the *seco* ester of symbiodinolide (4.5 mg, 100%) as a colorless solid that was sufficiently pure for the next stage. HRMS (ESI) calcd for $(M+2Na)^{2+}$ ($C_{69}H_{118}N_{0.5}Na_{1.5}O_{29}S_{0.5}$) m/z 1468.2481. Found 1468.2497.

3.8. Grubbs II complex-catalyzed cleavage of *seco* symbiodinolide (6) using NaClO

A solution of *seco* symbiodinolide (**6**) (3.4 mg, 1.17 μmol) in MeOH (0.3 mL) was degassed three times and then placed under an argon atmosphere. To the above stirred solution was added the second-generation Grubbs catalyst (29.4 mM in dichloromethane, 4 μL, 0.12 μmol) and sodium hypochlorite solution (3 μL, 7.9 μmol), and the mixture was stirred for 3 h at room temperature in the dark. The reaction mixture was concentrated in vacuo, and the residue was separated by RP-HPLC [Develosil ODS-HG-5, Ø 10×250 mm, Nomura Chemical Co., Aichi, Japan, 20–50% aqueous MeCN, 60 min linear gradient, flow rate 2.0 mL/min, RI detection] to give αβ,γδ-unsaturated aldehyde **7** (0.3 mg, 86%, t_R=9.13–10.07 min) and α,β-unsaturated aldehyde **8** (2.3 mg, 76%, t_R=25.93–29.87 min).

*3.8.1. αβ,γδ-Unsaturated aldehyde **7** (C1–C13 fragment).* ^{1}H NMR (CD_3OD) δ 1.74 (m, 2H), 2.44 (dd, J=8.7, 15.3 Hz, 1H), 2.47 and 2.52 (m, 2H), 2.56 (dd, J=4.6, 15.3 Hz, 1H), 3.66 (m, 1H), 3.67 (s, 3H, OMe), 3.81 (m, 1H), 3.89 (m, 1H), 4.23 (m, 1H), 6.09 (dd, J=7.8, 15.2 Hz, 1H), 6.46 (m, 2H), 7.29 (dd, J=10.1, 15.2 Hz, 1H), 9.49 (d, J=7.8 Hz, 1H); HR ESI-TOF-MS m/z 325.1194 $(M+Na)^+$, calcd for $C_{14}H_{22}O_7Na$: 325.1263.

*3.8.2. α,β-Unsaturated aldehyde **8** (C14–C25′ fragment).* A colorless solid; ^{1}H NMR (CD_3OD) δ 0.90 (t, J=6.9 Hz, 3H, H25′), 0.95 (d, J=6.4 Hz, 3H, C7′–Me), 1.01 (d, J=6.5 Hz, 3H, C53–Me), 1.06 (d, J=6.9 Hz, 3H, C95–Me), 1.16 (m, 2H, H84a), 1.25 (m, 1H, H90a), 1.29 (m, 2H, H24′), 1.30 (m, 2H, H23′), 1.31 (m, 2H, H22′), 1.33 (m, 2H, H21′), 1.42 (m, 2H, H19′), 1.45 (m, 2H, H96), 1.45 (s, 3H, C30–Me), 1.37 and 1.45 (m, 2H, H52), 1.50 (m, 2H, H20′), 1.51 (m, 2H, H80), 1.52 (m, 2H, H63), 1.53 (m, 2H, H78a, H92a), 1.38 and 1.58 (m, 4H, H86, H88), 1.59 (m, 4H, H82, H84b, H90b), 1.30 and 1.60 (m, 2H, H81), 1.62 (m, 1H, H74a), 1.66 (m, 2H, H45), 1.67 (m, 1H, H78b), 1.43 and 1.68 (m, 2H, H6′), 1.70 (s, 6H, C38–Me, C9′–Me), 1.70 (m, 2H, H62a, H92b), 1.59 and 1.72 (m, 2H, H50), 1.64 and 1.72 (m, 2H, H70), 1.54 and 1.87 (m, 2H, H85), 1.49 and 1.89 (m, 2H, H31), 1.94 (m, 3H, H62b, H89), 1.49 and 1.95 (m, 2H, H100), 1.49 and 1.97 (m, 2H, H16′), 2.06 (m, 2H, H74b, H95), 2.17 and 2.21 (m, 2H, H39), 2.23 (m, 4H, H43, H60), 2.17 and 2.26 (m, 2H, H35), 2.18 and 2.26 (m, 2H, H10′), 2.28 and 2.37 (m, 2H, H25), 2.42 (m, 2H, H2′), 2.43 (m, 1H, H53), 2.55 (m, 1H, H7′), 2.33 and 2.63 (m, 2H, H68), 2.65 (d, J=6.5 Hz, 1H, H29), 2.93 (dd, J=2.4, 6.2 Hz, 1H, H28), 2.98 (dd, J=2.4, 4.5 Hz, 1H, H27), 3.04 (t, J=8.6 Hz, 1H, H72), 3.12 (dd, J=1.7, 7.2 Hz, 1H, H94), 3.18 (m, 2H, H76, 98), 3.25 (m, 1H, H4′), 3.37 (m, 1H, H18′), 3.49 (m,

1H, H65), 3.51 (dd, J=3.5, 10.1 Hz, 1H, H14′), 3.56 (d, J=3.0 Hz, 1H, H12′), 3.59 (d, J=3.0 Hz, 1H, H102), 3.63 (m, 1H, H57), 3.64 (m, 1H, H26), 3.68 (m, 1H, H5′), 3.28 and 3.68 (m, 2H, H104), 3.69 (m, 2H, H64, H73), 3.73 (m, 2H, H15′, H17′), 3.75 (m, 2H, H44, H83), 3.77 (m, 1H, H51), 3.80 (m, 1H, H71), 3.81 (m, 1H, H61), 3.82 (m, 2H, H58, H11′), 3.84 (m, 2H, H79, H97), 3.89 (m, 1H, H75), 3.90 (m, 1H, H13′), 3.95 (m, 2H, H77, H91), 4.03 (m, 1H, H3′), 4.05 (m, 1H, H93), 4.11 (d, J=7.6 Hz, 1H, H66), 4.12 (m, 1H, H101), 4.19 (m, 2H, H40, H99), 4.20 (m, 1H, H32), 4.26 (m, 1H, H49), 4.27 (m, 2H, H46, H69), 4.36 (m, 2H, H36, H56), 4.87 (m, 1H, H59), 5.06 (d, J=9.2 Hz, 1H, H8′), 5.11 and 5.19 (br s, 2H, C67–CH_2a,b), 5.07 and 5.14 (m, 2H, H24), 5.21 (d, J=8.7 Hz, 1H, H37), 5.52 (dd, J=7.2, 13.6 Hz, 1H, H41), 5.55 (m, 2H, H33, H54), 5.63 (m, 1H, H34), 5.67 (m, 1H, H48), 5.68 (m, 2H, H42, H47), 5.74 (dd, J=6.4, 15.2 Hz, 1H, H55), 6.27 (dd, J=7.8, 15.6 Hz, 1H, H15), 6.98 (dd, J=4.6, 15.6 Hz, 1H, H16), 9.54 (d, J=7.8 Hz, 1H). HRMS (ESI) calcd for $(M+2Na)^{2+}$ ($C_{62}H_{106}N_{0.5}Na_{1.5}O_{25.5}S_{0.5}$) m/z 1316.1720. Found 1316.1758.

3.9. Grubbs II complex-catalyzed cleavage of *N-p*-BrBz palytoxin (9) using NaClO

A solution of *N-p*-BzBr palytoxin (**9**) (4.8 mg, 1.68 μmol) in MeOH (0.4 mL) was degassed three times and then placed under an argon atmosphere. To the above stirred solution was added the second-generation Grubbs catalyst (82.4 mM in dichloromethane, 10 μL, 0.82 μmol) and sodium hypochlorite solution (4 μL, 10.4 μmol), and the mixture was stirred for 5 h at room temperature in the dark. The reaction mixture was concentrated in vacuo, and the residue was separated by RP-HPLC [Develosil ODS-UG-5, Ø 10×250 mm, Nomura Chemical Co., Aichi, Japan, 30–70% aqueous MeCN, 80 min linear gradient, flow rate 2.0 mL/min, RI detection] to give two degradation products: *N-p*-bromobenzoyl aldehyde **10** (0.7 mg, 87%, t_R=10.41–11.20 min) and α,β-unsaturated aldehyde **11**.

*3.9.1. N-p-Bromobenzoyl aldehyde **10**.* ^{1}H NMR ($CDCl_3$) δ 1.41 (m, 1H), 1.51 (m, 1H), 1.77 (m, 1H), 1.80 (m, 3H), 1.89 (m, 1H), 2.15 (dd, J=6.4, 13.5 Hz,), 2.51 (ddd, J=1.4, 4.6, 16.3 Hz, 1H), 2.57 (ddd, J=2.8, 8.2, 16.3 Hz, 1H), 3.35 (m, 1H), 3.77 (m, 1H), 3.87 (m, 1H), 4.17 (m, 1H), 4.34 (m, 2H), 4.41 (m, 1H), 4.49 (m, 1H), 4.57 (t, J=5.9 Hz, 1H), 6.47 (br s, 1H, NH), 7.58 (d, J=8.7 Hz, 2H, Ph), 7.65 (d, J=8.7 Hz, 2H, Ph), 9.76 (br s, 1H); HR ESI-TOF-MS m/z 504.1005 $(M+Na)^+$, calcd for $C_{22}H_{28}BrNO_6Na$: 504.0998.

3.10. Grubbs II complex-catalyzed cleavage of pseurotin A

To a solution of pseurotin A (0.8 mg, 1.9 mmol, Enzo Life Sciences, NY) and *N*-methylmorpholine *N*-oxide (50% in MeOH, 10 mL, ca. 20 equiv) in MeOH (0.5 mL) was added a 0.01 M solution of second-generation Grubbs catalyst (19 μL, 0.1 equiv) in CH_2Cl_2. The solution was allowed to stand for 4 h at room temperature. The resultant mixture was directly subjected to preparative TLC (SiO_2, chloroform/methanol 9:1) to give the desired aldehyde **12** (0.6 mg) as a colorless oil, in ca. 90% yield.

3.10.1. α,β-Unsaturated aldehyde. ^{1}H NMR ($CDCl_3$) δ 1.98 (3H, s), 3.42 (3H, s), 4.00 (1H, br d, J=14 Hz), 4.65 (1H, d, J=14 Hz), 7.4–7.6, 8.2 (total 5H, arom.), 9.94 (1H, s); LC–MS 346.1 (M+H).

Acknowledgements

This work was supported in part by a Grant-in-Aid for Creative Scientific Research (16GS0206) from JSPS, and by the G-COE program in chemistry at Nagoya University from the Ministry of Education, Science, Sports and Culture, Japan.

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