DOI: 10.1002/ejoc.201301613

# Total Syntheses of Cochliomycin B and Zeaenol

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**Keywords:** Natural products / Total synthesis / Lactones / Coupling reactions / Metathesis

Divergent syntheses of two 14-membered resorcylic acid lactones (RALs), cochliomycin B (**6**) and zeaenol (**22**), have been accomplished. The key feature in our strategy was the facile construction of three contiguous stereogenic centers in the title molecules by using natural L-arabinose as the chiral template. The key reactions included Takai olefination, Suzuki cross coupling, transesterification, and a late-stage ring-closing metathesis (RCM).

## Introduction

Microorganisms have proved to be rich sources of bioactive secondary metabolites, and therefrom numerous compounds with potent biological activities and unique chemical structures have been discovered. Sharing the common core structural characteristics, β-resorcylic acid lactones (RALs) have been known for decades since the first isolation of radicicol (**1**, Figure 1)[1] followed by zearalenone,[2] (5*Z*)-7-oxozeaenol (**3,** or LL-Z1640-2),[3] and hypothemycin (**4**).[4] Interestingly, the original chemical structures proposed for radicicol and hypothemycin were mistakenly assigned, and even the original bioactivities of RALs did not solicit much interest from the bioorganic chemistry community, except for zearalenone, which was shown to have estrogen agonistic properties. From the early 1990s, especially after the discovery of the inhibitory activity of radicicol against HSP90,[5] RALs have undergone extensive bioactivity screening and revealed powerful biological activities with respect to antifungal,[6] antimalarial,[7] antiviral, and cytotoxic effects.[7,8] Furthermore, several members of this natural product family have been reported to be potent kinase and ATPase inhibitors.[9] For example, aigialomycin D (**2**; Figure 1) shows cytotoxicity in human cells through CDK/GSK-3 inhibition,[10] (5*Z*)-7-oxozeaenol (**3**) is an inhibitor of TAK-1,[11] and hypothemycin (**4**) has been reported to inhibit the *ras* signaling pathway.[12] Surprisingly, structurally similar radicicol and pochonin C[13] do not inhibit specific kinase, but rather the specific ATPase (HSP90) and HSV-helicase, respectively. Compounds **1** and **3**, on the other hand, have been shown to be competitive ligands for the ATP-binding pocket.[14,15]

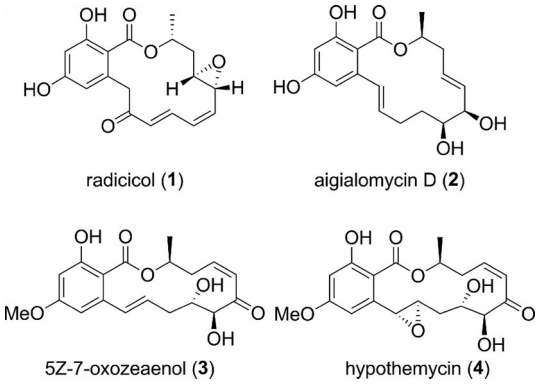


Figure 1. Typical RALs.

In 2011, Wang and co-workers[16] reported the isolation and structural determination of potent antifouling RALs from the culture broth of the fungus *Cochliobolus lunatus* from the South China Sea. Among the species showing antibacterial and cytotoxic activities, two new 14-membered resorcylic acid lactones with a rare natural acetonide group and one new 5-chloro-substituted lactone were discovered and named as cochliomycins A–C (**5**–**7**, respectively, in Figure 2),. Very recently, Nanda and co-workers completed the total synthesis of cochliomycin A (**5**)[17] and 5′-epi-cochliomycin C[18] taking advantage of Julia olefination in their strategy. A literature search revealed that numerous total syntheses of RALs have been reported,[19] but to the best of our knowledge no synthesis of cochliomycin B (**6**) has been presented so far. The high potential of finding new ATPase or kinase inhibitors from this class of species has encouraged us to design a modular diversity-oriented synthesis amenable to the preparation of libraries extending beyond the naturally available compounds. In this work cochliomycin B and zeaenol were used as targets to explore a practical approach towards our goal.

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Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201301613.

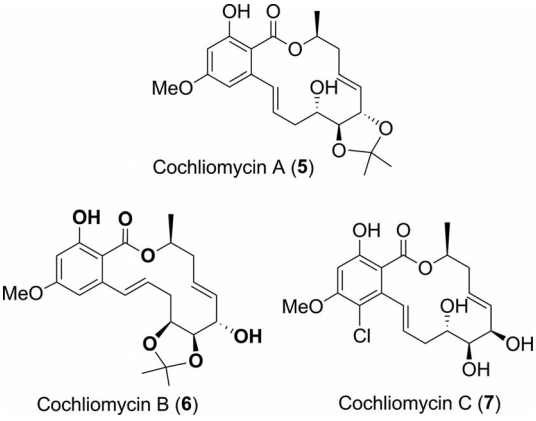
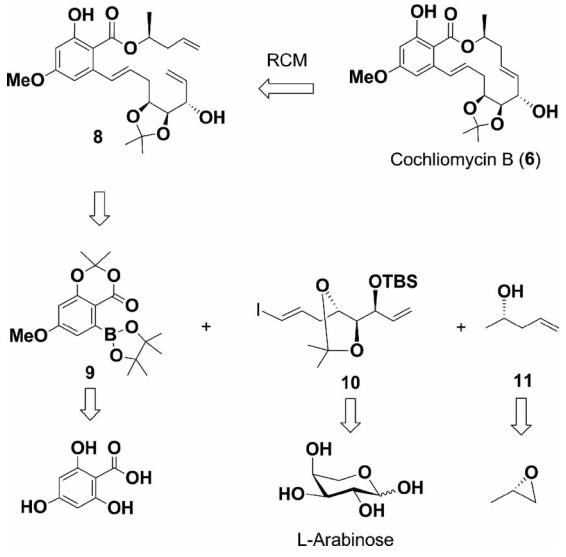



Figure 2. Structures of cochliomycins A–C.

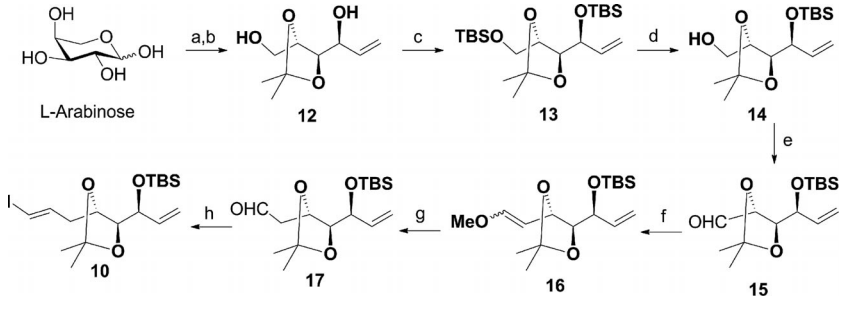
## Results and Discussion

The structure of cochliomycin B (**6**) consists of a resorcinol moiety fused to a 14-membered macrocyclic lactone ring that includes one methyl group, two *trans* double bonds, and three adjacent hydroxy groups. The retrosynthetic strategy to **6** is delineated in Scheme 1. Cochliomycin B (**6**) could be obtained from the advanced triene **8** through ring-closing metathesis (RCM), with **8** being constructed from arylborane **9**, vinyl iodide intermediate **10**, and (*S*)-pent-4-en-2-ol (**11**) successively by Suzuki cross-coupling and alkoxide-mediated transesterification. Note that the key intermediate vinyl iodide **10**, which contains three contiguous hydroxy groups, could be prepared from readily available L-arabinose with three inherent chiral centers.



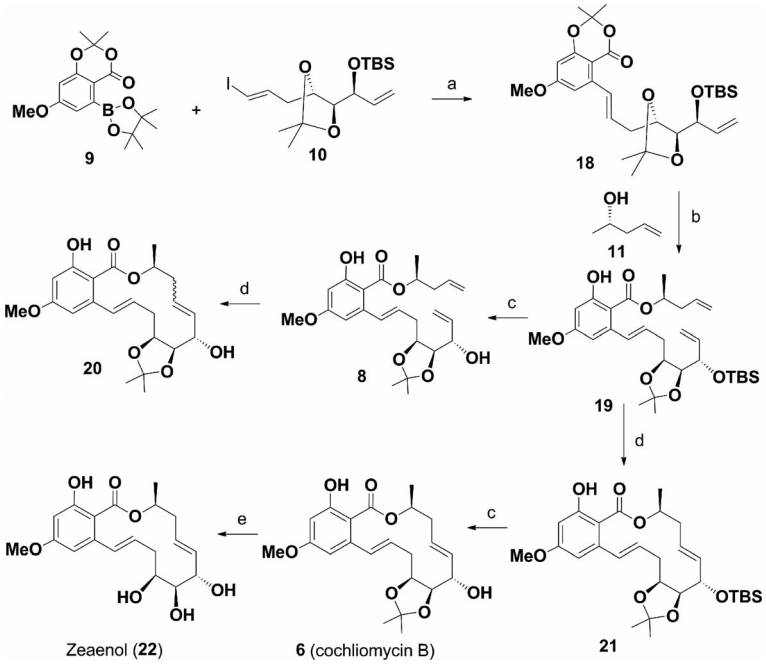

Scheme 1. Retrosynthetic analyses of cochliomycin B.

Fragments **9** and **11** are both known compounds. Fragment **9** was prepared from commercially available 2,4,6-trihydroxybenzoic acid over four steps according to a literature procedure[20] and fragment **11** was derived from the coupling reaction of (*S*)-propylene epoxide and vinylmagnesium bromide in the presence of catalytic CuI in dry THF.[21] The key intermediate for the whole target assembly, fragment **10**, was synthesized starting from natural L-arabinose in eight steps (Scheme 2). Thus, treatment of L-arabinose with 2,2-dimethoxypropane (DMOP) in dry *N*,*N*′-dimethylformamide (DMF) in the presence of a catalytic amount of *p*-toluenesulfonic acid (PTSA) afforded 3,4-*O*-isopropylidene-L-arabinopyranose in high yield.[22] Wittig reaction of this sugar hemiacetal intermediate with (methyl)triphenylphosphonium bromide in dry THF with *n*BuLi as the base afforded diol compound **12**. Selective blocking of the secondary hydroxy group of **12** was accomplished in two sequential steps, that is, full protection of **12** with TBSCl and imidazole in $CH_2Cl_2$ (→ **13**, yield 95%) followed by selective removal of the primary silyl ether in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS) in 95% ethanolic solution provided primary alcohol **14** in 81% yield.[23] Dess–Martin oxidation of the primary alcohol in **14** generated aldehyde **15**, which was subjected to homologation with (methoxymethyl)triphenylphosphorane in the presence of *t*BuOK to afford methyl enol ether **16** in 77% yield.[24] To our surprise, the subsequent hydrolysis of **16** with mercury acetate under previously reported reaction conditions[25] provided an unexpected elimination product (α,β-unsaturated aldehyde). By using a modified procedure,[26] we were pleased to find that treatment of the methyl enol ether **16** with mercury acetate at 0 °C in THF/$H_2O$ (v/v, 4:1) followed by the addition of 8% KI solution gave aldehyde **17** in 75% yield. Takai ole-




Scheme 2. Synthesis of fragment **10**. Reagents and conditions: a) DMOP, PTSA, DMF, 91%; b) $Ph_3PCH_3Br$, *n*BuLi, THF, 0 °C to room temp., 72%; c) TBSCl, imidazole, $CH_2Cl_2$, 95%; d) PPTS, 95% EtOH, 81%; e) Dess–Martin periodinane, $NaHCO_3$, $CH_2Cl_2$, 86%; f) $Ph_3PCH_2OMeCl$, *t*BuOK, THF, 0 °C to room temp., 77%; g) $Hg(OAc)_2$, THF/$H_2O$ (v/v, 4:1), 0 °C, then 8% KI, 75%; h) $CrCl_2$, $CHI_3$, THF, 0 °C, 65% (*E*/*Z* = 4.5:1).




Scheme 3. Syntheses of cochliomycin B (**6**) and zeaenol (**22**). Reagents and conditions: a) $[Pd(PPh_3)_4]$, $Cs_2CO_3$, THF/$H_2O$ (v/v, 10:1), 70 °C, 68%; b) **11**, NaH (60% in mineral oil), THF, 0 °C, 75%; c) TBAF, THF, 82% for **8**; 85% for **6**; d) Grubbs II catalyst, $CH_2Cl_2$, 40 °C, 67% for **21**; 42.5% for **20**; e) AcCl, MeOH, 91%.

fination[27] of the resulting **17** with $CrCl_2$ and $CHI_3$ in dry THF at 0 °C was carried out smoothly to furnish *trans*-vinyl iodide fragment **10**, albeit with a minor amount of the *cis*-vinyl iodide (65%, *E*/*Z* = 4.5:1, *J* = 14.4 Hz for *E*; *J* = 7.6 Hz for *Z*).

With all the required fragments in hand, we then focused our attention on the total synthesis of cochliomycin B (**6**) following the retrosynthetic analysis shown in Scheme 1. Accordingly, Suzuki cross-coupling of arylborane **9** and vinyl iodide **10** was investigated (Scheme 3) in THF/$H_2O$ (10:1) at 70 °C in the presence of a catalytic amount of $[Pd(PPh_3)_4]$ and 4 equiv. of $Cs_2CO_3$, affording compound **18** readily in a yield of 68%.[20c] The esterification of compound **18** and fragment **11** was initially explored in two conventional steps, that is, hydrolysis of compound **18** with 2 M aqueous LiOH followed by ester formation with alcohol **11** in the presence of condensation agents such as *N*′-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide (EDCI).[28] However, purification of the free acid from the hydrolysis products of compound **18** encountered difficulties with respect to purity and recovery due to its good hydrophilicity. Fortunately, transesterification[29] of **18** with the alkoxide anion derived from the treatment of fragment **11** with NaH in dry THF was carried out successfully presenting compound **19** in 75% yield. Desilylation of **19** with tetrabutylammonium fluoride (TBAF) in THF gave an 82% yield of **8**, which was subjected to ring-closing metathesis (RCM) under the standard conditions.[30] To our surprise, both *E* and *Z* isomeric olefins (*J* = 15.6 Hz for *E*; *J* = 10.8 Hz for *Z*) were formed in a ratio of about 1.55:1 under our RCM conditions, and it was very hard to obtain the pure *E* isomer (cochliomycin B) by routine column chromatography. A literature search revealed that the vast majority of RCM-based macrocyclizations provide *E*,*Z* mixtures, with the *E* isomer usually being favored.[31] In some cases,[32] RCM substrates having a free allylic alcohol gave low *E*,*Z* selectivity and reactivity, as exemplified by Poulsen and Madsen's results for the RCM of carbohydrate-derived enynes.[33] We also found that the *E*/*Z* selectivity differed slightly with reactant concentration, and the best result (**20**, based on $^1H$ NMR spectrum) was achieved by using the second-generation Grubbs catalyst at a concentration of $8 \times 10^{-4}$ M in $CH_2Cl_2$. According to the RCM mechanism described by Grubbs[34] and Hillier[35] and their co-workers, we envisaged that the bulky TBS-blocked allylic position might be a better substrate for the RCM reaction in favor of the *E* isomer. Consequently, compound **19** was directly treated with the Grubbs II catalyst in $CH_2Cl_2$ at 40 °C to afford 67% yield of the *E* isomer **21** exclusively.[36] Final removal of TBS from **21** with TBAF in THF gave natural cochliomycin B (**6**) in 85% yield. In addition, removal of the acetonide functionality from compound **6** was achieved by treatment of **6** with AcCl in methanol (1%) to afford another natural product zeaenol (**22**) in a yield of 91%. The analytical data ($^1H$, $^{13}C$ NMR, and optical rotation values) for both compounds **6** and **22** are consistent with those of the natural products.

## Conclusions

Cochliomycin B (**6**) and zeaenol (**22**) have been synthesized from natural chiral template L-arabinose in overall yields of 4.8 and 4.3%, respectively, by Takai olefination,

Suzuki coupling, alkoxide-mediated transesterification, and RCM macrocyclization as the crucial steps. The syntheses of other structurally related RALs and studies on their biological activities are under way in our laboratory and the results will be reported in due course.

## Experimental Section

**General Methods:** All reactions involving air- and moisture-sensitive reagents were carried out under nitrogen. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF was distilled from Na and benzophenone. Dried $CH_2Cl_2$ and DMF were treated with $CaH_2$. Column chromatography was carried out by using silica gel (100–120 mesh). Routine monitoring of reactions was carried out by using silica gel 60 F254 TLC plates. Optical rotations were measured with a WZZ-2SS automatic digital polarimeter. $^1H$ and $^{13}C$ NMR spectra were recorded with a Bruker AVANCE-III (400 MHz) spectrometer. Chemical shifts are given in ppm using $Me_4Si$ ($\delta$ = 0 ppm) as internal standard and coupling constants ($J$) are reported in Hz. HRMS were measured with a Bruker micro-TOF Q II mass spectrometer. IR spectra were recorded using KBr with a NICOLET 8700 infrared spectrometer.

**(*S*)-1-[(4*R*,5*S*)-5-(Hydroxymethyl)-2,2-dimethyl-1,3-dioxolan-4-yl]-prop-2-en-1-ol (12):** PTSA monohydrate (375 mg, 1.974 mmol) and 2,2-dimethoxypropane (DMOP; 62.5 mL, 0.508 mol) were added to a stirred solution of L-arabinose (25 g, 0.166 mol) in dry DMF (50 mL). The mixture was stirred at room temp. for 2 h and then neutralized with $Et_3N$ (1 mL). The mixture was concentrated in vacuo and the residue purified by silica gel chromatography (EtOAc/petroleum ether, 2:1) to give 3,4-*O*-isopropylidene-β-L-arabinopyranose (28.8 g, 91%) as a white solid. *n*BuLi (34 mL, 2.5 M in hexane, 0.085 mol) was added to a suspension of (methyl)triphenylphosphonium bromide (30 g, 0.084 mol) in dry THF (100 mL) at 0 °C. After 1 h, 3,4-*O*-isopropylidene-β-L-arabinopyranose (4.5 g, 0.024 mol) in THF (20 mL) was added dropwise to the above yellow suspension. The mixture was gradually warmed to room temp. with stirring. After 48 h, the mixture was quenched with saturated aqueous $NH_4Cl$ (30 mL) at 0 °C, then extracted with EtOAc (3× 50 mL). The combined organic solvents were concentrated under reduced pressure and the orange residue purified by silica gel chromatography (EtOAc/petroleum ether, 1:1) to afford **12** (3.2 g, 72%) as a colorless oil. $[\alpha]_D^{25}$ = –9.8 ($c$ = 0.75, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 5.92 (ddd, $J$ = 16.8, 10.4, 6.0 Hz, 1 H), 5.40 (d, $J$ = 17.2 Hz, 1 H), 5.27 (d, $J$ = 10.4 Hz, 1 H), 4.27–4.23 (m, 2 H), 4.14 (dd, $J$ = 6.4, 4.4 Hz, 1 H), 3.81–3.79 (m, 2 H), 2.73 (br., 2 H), 1.52 (s, 3 H), 1.38 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 137.06, 117.49, 108.60, 79.25, 77.30, 70.40, 61.15, 27.36, 25.03 ppm. IR: $\tilde{\nu}$ = 3390, 2989, 2936, 2889, 1646 $cm^{-1}$. HRMS (ESI): calcd. for $C_9H_{16}O_4Na$ $[M + Na]^+$ 211.0946; found 211.0982.

***tert*-Butyl{[(4*S*,5*S*)-5-{(*S*)-1-[(*tert*-butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolan-4-yl]methoxy}dimethylsilane (13):** Imidazole (7.16 g, 0.105 mol) and TBSCl (5.265 g, 0.035 mol) were added to a solution of compound **12** (3 g, 0.016 mol) in $CH_2Cl_2$ (20 mL). After 2 h the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (10 mL), extracted with $CH_2Cl_2$ (2× 10 mL), washed with brine, and the solvents evaporated in vacuo. Column chromatography of the residue on silica gel (EtOAc/petroleum ether, 1:50) yielded **13** (6.3 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ = +35.5 ($c$ = 0.22, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.05 (ddd, $J$ = 17.2, 10.8, 4.8 Hz, 1 H), 5.35 (dt, $J$ = 17.2, 2.0 Hz, 1 H), 5.15 (dt, $J$ = 10.8, 2.0 Hz, 1 H), 4.39–4.35 (m, 1 H), 4.12 (q, $J$ = 6.0 Hz, 1 H), 3.98 (t, $J$ = 6.8 Hz, 1 H), 3.87 (dd, $J$ = 10.8, 6.0 Hz, 1 H), 3.69 (dd, $J$ = 11.2, 5.6 Hz, 1 H), 1.44 (s, 3 H), 1.32 (s, 3 H), 0.91 (s, 9 H), 0.89 (s, 9 H), 0.07 (s, 6 H), 0.06 (s, 6 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 138.03, 115.60, 108.07, 80.82, 78.28, 72.20, 62.38, 27.65, 26.04, 25.95, 25.42, 18.51, 18.46, –4.42, –4.65, –5.24, –5.28 ppm. IR: $\tilde{\nu}$ = 2959, 2936, 2860, 1646, 1473 $cm^{-1}$. HRMS (ESI): calcd. for $C_{21}H_{44}O_4Si_2Na$ $[M + Na]^+$ 439.2676; found 439.2714.

**[(4*S*,5*S*)-5-{(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolan-4-yl]methanol (14):** A solution of **13** (3 g, 7.2 mmol) in 95% ethanol (20 mL) was treated with PPTS (210 mg, 0.835 mmol). The reaction was monitored by TLC until all starting material had disappeared. Then $Et_3N$ (0.5 mL) was added to neutralize the acid and the solution concentrated under reduced pressure. Purification of the residue by silica gel chromatography (EtOAc/petroleum ether, 1:3) yielded **14** (1.764 g, 81%) as a colorless oil. $[\alpha]_D^{25}$ = –93 ($c$ = 0.8, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 6.03 (ddd, $J$ = 17.2, 10.8, 4.8 Hz, 1 H), 5.35 (dt, $J$ = 17.2, 2.0 Hz, 1 H), 5.22 (dt, $J$ = 10.4, 2.0 Hz, 1 H), 4.38–4.34 (m, 1 H), 4.28 (q, $J$ = 6.4 Hz, 1 H), 4.18 (t, $J$ = 6.4 Hz, 1 H), 3.89–3.83 (m, 1 H), 3.72–3.68 (m, 1 H), 2.69 (br., 1 H), 1.47 (s, 3 H), 1.35 (s, 3 H), 0.91 (s, 9 H), 0.10 (s, 3 H), 0.08 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 136.85, 116.70, 108.58, 79.49, 78.21, 73.15, 61.13, 27.48, 25.96, 25.20, 18.44, –4.60, –4.79 ppm. IR: $\tilde{\nu}$ = 3346, 2939, 2857, 1464 $cm^{-1}$. HRMS (ESI): calcd. for $C_{15}H_{30}O_4SiNa$ $[M + Na]^+$ 325.1811; found 325.1811.

**(4*R*,5*S*)-5-{(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (15):** $NaHCO_3$ (1.176 g, 14.01 mmol) and Dess–Martin periodinane (1.98 g, 4.67 mmol) were sequentially added to a solution of compound **14** (950 mg, 3.144 mmol) in $CH_2Cl_2$ (15 mL). The mixture was stirred for 1 h and then poured into cold water (10 mL). The organic layer was separated and the aqueous phase extracted with $CH_2Cl_2$ (2× 30 mL). The combined organic layers were evaporated in vacuo and the residue purified by silica gel chromatography (EtOAc/petroleum ether, 1:16) to afford **15** (811 mg, 86%) as a yellowish oil. $[\alpha]_D^{25}$ = +72 ($c$ = 0.85, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 9.73 (d, $J$ = 2.0 Hz, 1 H), 5.94 (ddd, $J$ = 17.2, 10.4, 2.8 Hz, 1 H), 5.26 (dt, $J$ = 17.6, 1.6 Hz, 1 H), 5.18 (dt, $J$ = 10.4, 1.6 Hz, 1 H), 4.40 (dd, $J$ = 7.6, 2.0 Hz, 1 H), 4.34 (dd, $J$ = 7.6, 4.0 Hz, 1 H), 4.27–4.26 (m, 1 H), 1.56 (s, 3 H), 1.35 (s, 3 H), 0.87 (s, 9 H), 0.03 (s, 3 H), 0.02 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 200.30, 137.30, 117.58, 110.89, 83.02, 81.41, 72.62, 26.81, 26.00, 25.21, 18.30, –3.72, –4.59 ppm. IR: $\tilde{\nu}$ = 2930, 2860, 1737, 1646, 1467 $cm^{-1}$. HRMS (ESI): calcd. for $C_{15}H_{28}O_4SiNa$ $[M + Na]^+$ 323.1655; found 323.1615.

***tert*-Butyl({(*S*)-1-[(4*S*,5*S*)-5-(2-methoxyvinyl)-2,2-dimethyl-1,3-dioxolan-4-yl]allyl}oxy)dimethylsilane (16):** *t*BuOK (0.556 g, 4.95 mmol) was added to a suspension of (methoxymethyl)triphenylphosphonium chloride (1.34 g, 3.91 mmol) in dry THF (12 mL) at 0 °C. The mixture was stirred for 45 min and a solution of aldehyde **15** (1.0 g, 3.33 mmol) in THF (8 mL) was added. After 1 h, the mixture was quenched with saturated aqueous $NH_4Cl$ (5 mL), extracted with EtOAc (2× 20 mL), and dried. Removal of the solvent gave an oil which was subjected to silica gel flash column chromatography (EtOAc/petroleum ether, 1:16) to provide methyl enol ether **16** (842 mg, *E*,*Z* mixture, 77%) as a colorless oil.

**2-[(4*S*,5*S*)-5-{(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolan-4-yl]acetaldehyde (17):** The methyl enol ether **16** (400 mg, 1.218 mmol) was dissolved in THF (40 mL) at 0 °C and

then mercuric acetate (956 mg, 2.686 mmol) in cooled water (10 mL) was added dropwise. The suspension was stirred for 1 h and then 8% aqueous KI solution (10 mL) was then added to quench the reaction. The reaction mixture was extracted with EtOAc (3× 20 mL) and the combined organic solvents were dried with anhydrous $Na_2SO_4$ and concentrated in vacuo to afford the crude aldehyde. Purification on silica gel (EtOAc/petroleum ether, 1:16) afforded **17** (287 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = –148 (*c* = 0.3, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 9.77 (s, 1 H), 5.99–5.92 (m, 1 H), 5.32 (dd, *J* = 17.2, 1.2 Hz, 1 H), 5.22 (dd, *J* = 10.8, 1.2 Hz, 1 H), 4.70–4.64 (m, 1 H), 4.23–4.21 (m, 1 H), 4.13–4.10 (m, 1 H), 2.89–2.83 (m, 2 H), 1.47 (s, 3 H), 1.35 (s, 3 H), 0.89 (d, *J* = 1.6 Hz, 9 H), 0.07 (dd, *J* = 2.0 Hz, 6 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 200.76, 137.14, 117.01, 108.75, 79.56, 73.27, 72.16, 44.16, 27.46, 26.04, 25.41, 18.48, –4.38, –4.64 ppm. IR: $\tilde{\nu}$ = 2936, 2857, 1725, 1655, 1473 cm$^{-1}$. HRMS (ESI): calcd. for $C_{16}H_{30}O_4SiNa$ $[M + Na]^+$ 337.1811; found 337.1775.

***tert*-Butyl{[(*S*)-1-{(4*S*,5*S*)-5-[(*E*)-3-iodoallyl]-2,2-dimethyl-1,3-dioxolan-4-yl}allyl]oxy}dimethylsilane (10):** Anhydrous $CrCl_2$ (626 mg, 5.088 mmol) was suspended in dry THF (15 mL) under nitrogen. A solution of aldehyde **17** (200 mg, 0.636 mmol) and iodoform (752 mg, 1.908 mmol) in THF (8 mL) was then added dropwise to the suspension at 0 °C. After stirring at 0 °C for 3 h, the reaction mixture was poured into water (10 mL), extracted with diethyl ether (3× 25 mL), and evaporated in vacuo. The residue was purified by silica gel chromatography (EtOAc/petroleum ether, 1:250) to afford vinyl iodide **10** (181 mg, 65%) as a colorless oil. $[\alpha]_D^{25}$ = –150 (*c* = 0.6, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 6.59 (dt, *J* = 14.4, 7.2 Hz, 1 H), 6.09 (d, *J* = 14.4 Hz, 1 H), 5.91 (ddd, *J* = 16.8, 10.4, 5.6 Hz, 1 H), 5.32 (d, *J* = 17.6 Hz, 1 H), 5.19 (d, *J* = 10.4 Hz, 1 H), 4.22 (t, *J* = 6.4 Hz, 1 H), 4.11–4.07 (m, 1 H), 3.99 (t, *J* = 6.4 Hz, 1 H), 2.41–2.36 (m, 2 H), 1.47 (s, 3 H), 1.33 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 3 H), 0.07 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 143.21, 137.24, 116.93, 108.48, 80.54, 76.38, 72.95, 36.74, 27.87, 26.03, 25.68, 18.50, –4.32, –4.54 ppm. IR: $\tilde{\nu}$ = 2933, 2857, 1614, 1470 cm$^{-1}$. HRMS (ESI): calcd. for $C_{17}H_{31}O_3ISiNa$ $[M + Na]^+$ 461.0985; found 461.0964.

**5-{(*E*)-3-[(4*S*,5*S*)-5-{(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-1-en-1-yl}-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (18):** Degassed solvent ($THF/H_2O$, 10:1, 11 mL) was added under nitrogen to a mixture of vinyl iodide **10** (144 mg, 0.328 mmol), boronate **9** (141 mg, 0.422 mmol), $Cs_2CO_3$ (426 mg, 1.308 mmol), and $[Pd(PPh_3)_4]$ (cat.). The solution was heated at 70 °C for 2 h (monitoring with TLC). After cooling to room temp., saturated aqueous $NH_4Cl$ (5 mL) was added and the mixture extracted with EtOAc (3× 10 mL). The organic layer was dried with $Na_2SO_4$ and then concentrated to dryness. The residue was purified by silica gel column chromatography (EtOAc/petroleum ether, 1:6) to afford **18** (116 mg, 68%) as a yellowish oil. $[\alpha]_D^{25}$ = –163.3 (*c* = 0.6, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.51 (d, *J* = 16.0 Hz, 1 H), 6.79 (d, *J* = 2.4 Hz, 1 H), 6.33 (d, *J* = 2.4 Hz, 1 H), 6.27 (dt, *J* = 17.6, 7.2 Hz, 1 H), 5.93 (ddd, *J* = 16.8, 10.4, 6.0 Hz, 1 H), 5.37 (d, *J* = 17.6 Hz, 1 H), 5.21 (d, *J* = 10.4 Hz, 1 H), 4.29 (t, *J* = 6.8 Hz, 1 H), 4.20 (ddd, *J* = 9.6, 5.6, 4.0 Hz, 1 H), 4.01 (t, *J* = 6.0 Hz, 1 H), 3.84 (s, 3 H), 2.63–2.57 (m, 2 H), 1.69 (s, 6 H), 1.51 (s, 3 H), 1.35 (s, 3 H), 0.91 (s, 9 H), 0.11 (s, 3 H), 0.08 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 164.93, 160.43, 158.84, 144.01, 137.38, 135.39, 131.67, 130.31, 117.04, 108.44, 108.38, 105.13, 103.88, 100.47, 81.12, 77.40, 72.97, 55.81, 34.04, 29.88, 28.02, 26.08, 25.90, 25.83, 25.80, 18.56, –4.23, –4.46 ppm. IR: $\tilde{\nu}$ = 2927, 2854, 1734, 1608, 1576 cm$^{-1}$. HRMS (ESI): calcd. for $C_{28}H_{42}O_7SiNa$ $[M + Na]^+$ 541.2597; found 541.2603.

**(*S*)-Pent-4-en-2-yl 2-{(*E*)-3-[(4*S*,5*S*)-5-{(*S*)-1-[(*tert*-Butyldimethylsilyl)oxy]allyl}-2,2-dimethyl-1,3-dioxolan-4-yl]prop-1-en-1-yl}-6-hydroxy-4-methoxybenzoate (19):** To a solution of pent-4-en-2-ol (**11**; 90 mg, 1.046 mmol) in dry THF was added NaH (62 mg, 60% in mineral oil, 1.55 mmol) under nitrogen at 0 °C. The reaction mixture was stirred at this temperature for 30 min and then a solution of **18** (100 mg, 0.193 mmol) in THF (5 mL) was added to the above suspension. Saturated aqueous $NH_4Cl$ (2 mL) was added to quench the reaction until TLC showed completion of the reaction (about 4 h). The mixture was extracted with EtOAc (3× 5 mL), concentrated under reduced pressure, and the residue purified by silica gel column chromatography (EtOAc/petroleum ether, 1:25) to afford **19** (79 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = –59.4 (*c* = 0.65, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 11.74 (s, 1 H), 7.04 (d, *J* = 15.6 Hz, 1 H), 6.48 (d, *J* = 2.8 Hz, 1 H), 6.38 (d, *J* = 2.4 Hz, 1 H), 6.04–5.92 (m, 2 H), 5.86–5.76 (m, 1 H), 5.35 (d, *J* = 17.6 Hz, 1 H), 5.27–5.20 (m, 2 H), 5.15–5.10 (m, 2 H), 4.28–4.27 (m, 1 H), 4.18 (ddd, *J* = 9.6, 6.0, 3.6 Hz, 1 H), 4.03 (t, *J* = 6.0 Hz, 1 H), 3.81 (s, 3 H), 2.63–2.38 (m, 4 H), 1.50 (s, 3 H), 1.35 (d, *J* = 6.4 Hz, 3 H), 1.34 (s, 3 H), 0.92 (s, 9 H), 0.10 (s, 3 H), 0.09 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.92, 165.13, 164.11, 143.51, 137.62, 133.52, 133.32, 129.15, 118.40, 116.70, 108.52, 108.30, 104.21, 99.96, 80.72, 73.30, 72.00, 55.60, 40.38, 33.73, 29.89, 27.88, 26.07, 25.71, 19.79, 18.52, –4.28, –4.51 ppm. IR: $\tilde{\nu}$ = 2933, 2857, 1743, 1649, 1611, 1581 cm$^{-1}$. HRMS (ESI): calcd. for $C_{30}H_{46}O_7SiNa$ $[M + Na]^+$ 569.2911; found 569.2890.

**(S)-Pent-4-en-2-yl 2-Hydroxy-6-[(*E*)-3-{(4*S*,5*R*)-5-[(*S*)-1-hydroxyallyl]-2,2-dimethyl-1,3-dioxolan-4-yl}prop-1-en-1-yl]-4-methoxybenzoate (8):** A solution of **19** (90 mg, 0.165 mmol) in THF (5 mL) was treated with TBAF (60 mg, 0.189 mmol) at room temp. After the starting material had disappeared, the solvent was removed and the residue subjected directly to silica gel column chromatography (EtOAc/petroleum ether, 1:3) to afford **8** (58 mg, 82%) as a colorless oil. $[\alpha]_D^{25}$ = +33.3 (*c* = 0.3, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 11.74 (s, 1 H), 7.07 (d, *J* = 15.6 Hz, 1 H), 6.45 (d, *J* = 2.4 Hz, 1 H), 6.39 (d, *J* = 2.8 Hz, 1 H), 5.95–5.78 (m, 3 H), 5.42 (d, *J* = 17.6 Hz, 1 H), 5.30–5.23 (m, 2 H), 5.16–5.10 (m, 2 H), 4.30–4.27 (m, 1 H), 4.22–4.21 (m, 1 H), 4.07 (t, *J* = 5.6 Hz, 1 H), 3.82 (s, 3 H), 2.68–2.62 (m, 1 H), 2.56–2.40 (m, 3 H), 2.36 (d, *J* = 5.6 Hz, 1 H), 1.53 (s, 3 H), 1.38 (s, 3 H), 1.36 (d, *J* = 6.4 Hz, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 170.72, 165.11, 164.04, 143.19, 137.37, 133.75, 133.44, 128.03, 118.32, 117.57, 108.51, 108.33, 104.18, 99.95, 79.89, 71.99, 70.83, 55.49, 40.26, 33.81, 27.70, 25.18, 19.72 ppm. IR: $\tilde{\nu}$ = 3440, 2924, 2851, 2320, 1728, 1461 cm$^{-1}$. HRMS (ESI): calcd. for $C_{24}H_{32}O_7Na$ $[M + Na]^+$ 455.2046; found 455.2039.

**(3a*S*,4*S*,5*E*,8*S*,15*E*,17a*S*)-4-(*tert*-Butyldimethylsilyloxy)-11-hydroxy-13-methoxy-2,2,8-trimethyl-7,8,17,17a-tetrahydro-3a*H*-benzo[*c*][1,3]dioxolo[4,5-*h*][1]oxacyclotetradecin-10(4*H*)-one (21):** The second-generation Grubbs catalyst (12 mg, 0.015 mmol) was added to a solution of **19** (60 mg, 0.11 mmol) in degassed dry $CH_2Cl_2$ (180 mL). The mixture was stirred at 40 °C for 12 h, the solvent was removed under reduced pressure, and the residue purified by silica gel column chromatography (EtOAc/petroleum ether, 1:25) to afford **21** (38.1 mg, 67%) as a colorless oil. $[\alpha]_D^{25}$ = –112.2 (*c* = 0.18, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 11.69 (s, 1 H), 6.88 (d, *J* = 15.6 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 6.37 (d, *J* = 2.4 Hz, 1 H), 5.86 (ddd, *J* = 15.2, 7.6, 4.8 Hz, 1 H), 5.76 (ddd, *J* = 15.2, 7.2, 4.0 Hz, 1 H), 5.56 (dd, *J* = 15.6, 8.0 Hz, 1 H), 5.39–5.35 (m, 1 H), 4.28 (t, *J* = 8.4 Hz, 1 H), 4.15–4.11 (m, 1 H), 3.99 (dd, *J* = 8.8, 5.2 Hz, 1 H), 3.81 (s, 3 H), 2.68–2.44 (m, 4 H), 1.49 (s, 3 H), 1.42 (d, *J* = 6.4 Hz, 3 H), 1.36 (s, 3 H), 0.86 (s, 9 H), 0.09 (s, 3 H), 0.05 (s, 3 H) ppm. $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ =

171.04, 165.08, 164.16, 143.27, 133.48, 132.98, 128.98, 128.10, 107.82, 104.33, 100.16, 81.21, 73.02, 70.93, 55.49, 37.81, 34.13, 28.61, 26.07, 25.90, 19.13, 18.35, –3.99, –4.11 ppm. IR: $\tilde{\nu}$ = 2936, 2854, 1649, 1608, 1467 $cm^{-1}$. HRMS (ESI): calcd. for $C_{28}H_{42}O_7SiNa$ $[M + Na]^+$: 541.2597; found 541.2578.

**Cochliomycin B (6)**

**Method A:** Compound **8** (40 mg, 0.092 mmol) was dissolved in dry degassed DCM (116 mL, $c = 8.0 \times 10^{-4}$ M), the solution was treated with the second-generation Grubbs catalyst (8.5 mg, 0.01 mmol), and the mixture was stirred at 40 °C for 4 h. Then the solvent was removed under reduced pressure and the residue was purified by HPLC to afford **20** [15.9 mg, 42.5%; *E*/*Z* ≈ 1.55:1 based on the $^1H$ NMR spectrum: $J$ = 15.6 Hz for *E*, $J$ = 10.8 Hz for *Z*; the *E* enantiomer is cochliomycin B (**6**)].

**Method B:** TBAF (60 mg, 0.186 mmol) was added to a solution of compound **21** (60 mg, 0.116 mmol) in THF (5 mL) at room temp. After completion of the reaction, the solvent was removed under reduced pressure and the residue purified by silica gel column chromatography (EtOAc/petroleum ether, 1:3) to afford pure **6** (39.8 mg, 85%) as an amorphous solid. $[\alpha]_D^{25}$ = +38.8 ($c$ = 0.08, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 11.52 (s, 1 H), 7.01 (dd, $J$ = 16.0, 2.4 Hz, 1 H), 6.41 (d, $J$ = 2.4 Hz, 1 H), 6.39 (d, $J$ = 2.4 Hz, 1 H), 6.08 (ddd, $J$ = 15.2, 9.2, 4.4 Hz, 1 H), 5.65 (ddd, $J$ = 15.2, 9.2, 3.6 Hz, 1 H), 5.48–5.42 (m, 2 H), 4.36 (ddd, $J$ = 11.6, 4.4, 3.2 Hz, 1 H), 4.12 (t, $J$ = 8.8 Hz, 1 H), 3.86 (dd, $J$ = 10.0, 4.8 Hz, 1 H), 3.82 (s, 3 H), 3.03 (s, 1 H), 2.75–2.74 (m, 1 H), 2.63–2.58 (m, 1 H), 2.55–2.45 (m, 1 H), 2.45–2.40 (m, 1 H), 1.53 (s, 3 H), 1.45 (d, $J$ = 6.4 Hz, 3 H), 1.42 (s, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 170.63, 164.83, 164.11, 142.60, 134.53, 132.90, 130.48, 126.30, 107.90, 107.67, 104.58, 100.15, 79.54, 70.60, 69.74, 55.52, 38.30, 31.38, 28.47, 25.96, 18.86 ppm. IR: $\tilde{\nu}$ = 3440, 2930, 2851, 2381, 2326, 1631 $cm^{-1}$. HRMS (ESI): calcd. for $C_{22}H_{27}O_7$ $[M - H]^-$ 403.1757; found 403.1773.

**Zeaenol (22):** Compound **6** (30 mg, 0.074 mmol) in MeOH (2 mL) was treated with acetyl chloride (20 μL) for about 10 h, at the end of which time TLC showed the complete consumption of the starting material. The solution was evaporated in vacuo and the residue purified by silica gel column chromatography (EtOAc/petroleum ether, 3:2) to give zeaenol as a white powder (24.6 mg, 91%). $[\alpha]_D^{25}$ = –95 ($c$ = 0.42, MeOH). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 11.85 (s, 1 H), 7.11 (d, $J$ = 15.6 Hz, 1 H), 6.43 (d, $J$ = 2.4 Hz, 1 H), 6.39 (d, $J$ = 2.4 Hz, 1 H), 6.00–5.95 (m, 1 H), 5.86–5.80 (m, 1 H), 5.74–5.70 (m, 1 H), 5.34–5.30 (m, 1 H), 4.27 (m, 1 H), 3.98 (m, 1 H), 3.81 (s, 3 H), 3.61–3.58 (m, 1 H), 2.60 (br., 3 H), 2.55–2.24 (m, 4 H), 1.46 (d, $J$ = 6.0 Hz, 3 H) ppm. $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 171.34, 165.41, 164.16, 142.99, 133.82, 131.74, 129.29, 128.60, 107.72, 104.04, 100.22, 73.27, 71.55, 55.50, 37.96, 36.11, 19.77 ppm. IR: $\tilde{\nu}$ = 3442, 2932, 2851, 1696, 1597 $cm^{-1}$. HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$ 387.1420; found 387.1399.

**Supporting Information** (see footnote on the first page of this article): $^1H$ and $^{13}C$ NMR spectra for all new compounds and H–H COSY for cochliomycin B and zeaenol.

## Acknowledgments

This work was supported in part by the National Basic Research Program of China (grant number 2012CB822101), the National Innovative Drug Fundation (project number 2012ZX09502001), and the National Natural Science Foundation of China (NSFC) (NSF of China; projects numbers 21072217 and 21232002).

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Received: October 28, 2013
Published Online: January 28, 2014

  