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Stereoselective total synthesis of cochliomycin A

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ABSTRACT

A convergent and stereoselective synthesis of cochliomycin A, a 14-membered resorcyclic acid lactone, based on chiron approach is described. The key reactions involved olefin cross-metathesis and sodium hydride promoted one-pot intramolecular lactonization. L-Arabinose was used as a chiral pool material for the construction of the key fragment.

1. Introduction

In recent years, resorcylic acid lactones (RALs) have gained considerable attention, as many of them possess remarkable and diverse biological activities.[1] Cochliomycin A–C (**1**–**3**, Fig. 1), three new 14-membered resorcyclic acid lactones, together with the known zeaenol (**4**), were isolated from the culture broth of *Cochliobolus lunatus* in 2011.[2]

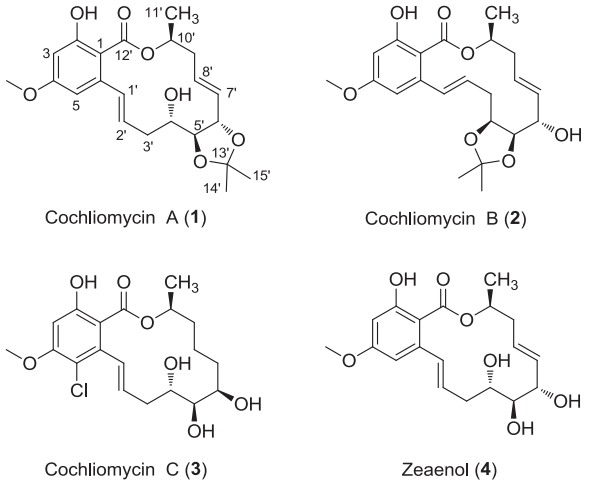

Fig. 1. Structures of cochliomycin A–C (**1**–**3**) and zeaenol (**4**).

The cochliomycin A (**1**) and B (**2**) comprised similar 14-membered resorcyclic acid lactone skeleton with a rare natural acetonide group. The relative configurations of cochliomycin A and B were established on the basis of extensive spectroscopic analysis including 1D NOE and 2D NOESY experiments. The only difference between these two compounds is the acetonide group, which has never been found before in any natural resorcylic acid lactone. The absolute configurations of cochliomycin A and B were further confirmed by treatment of zeaenol (**4**) with 2,2-dimethoxypropane in the presence of *p*-toluenesulfonic acid (PTSA) resulted in a mixture of cochliomycin A and B. Cochliomycin A was found to show potent antifouling activity against the larval settlement of the barnacle *Balanus amphitrite* and moderate antibacterial activity against *Staphylococcus aureus*. It is noteworthy that the unusual acetonide moiety in cochliomycin A probably contributes to the antifouling activity because cochliomycin A showed better antifouling activity with EC_{50} value (1.2 μg/mL), approximately threefold over zeaenol (**4**) (5.0 μg/mL).

Due to its novel structure and potent biological activity, cochliomycin A constitutes an ideal target for total synthesis. Very recently, cochliomycin A was firstly synthesized by Nanda's group from L-(+)-tartaric acid in 6.5% overall yields employing Keck allylation, Julia–Kocienski olefination and a late-stage RCM reaction as the key steps.[3] As part of our interest in the total synthesis of various complex natural products based on carbohydrate skeletons,[4] we herein report a convergent total synthesis of cochliomycin A using L-arabinose as the chiral pool material.

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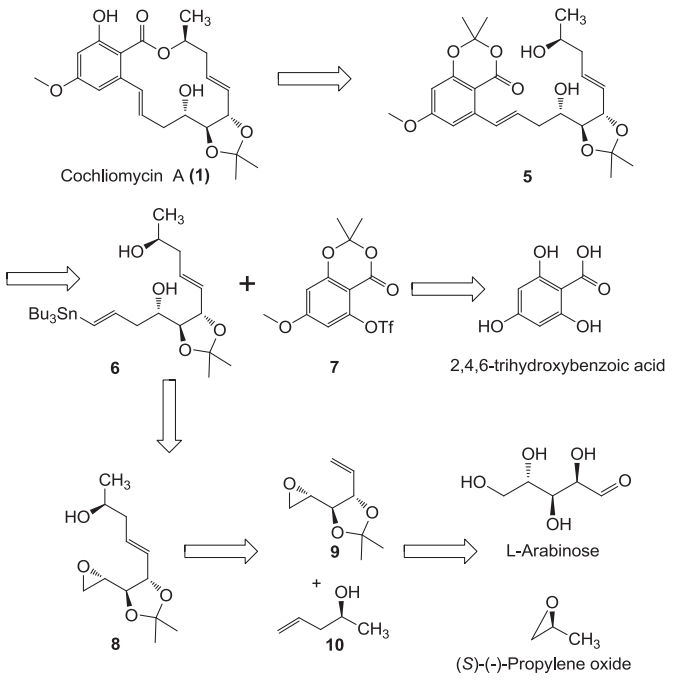
Our retrosynthesis analysis of cochliomycin A is summarized in Scheme 1. To construct the 14-membered macrocyclic core, we planned to utilize macrolactonization of the precursor **5**, which could be obtained by Stille coupling between the stannane **6** and the known triflate **7**. The key intermediate **6** could be obtained from the epoxide **8** via an easy reaction sequence. The *trans* olefin moiety at C7′/C8′ in **8** could be installed by olefin cross-metathesis of the epoxide **9** and the olefinic side chain **10**, which could be accessible readily from L-arabinose and (*S*)-(−)-propylene oxide, respectively. This approach was based on the fact that the three desired continuous stereogenic centers in the cochliomycin A (**1**) could directly be mapped onto natural L-arabinose.



Scheme 1. Retrosynthetic analysis of cochliomycin A (**1**).

2. Results and discussion

Accordingly, the synthesis of the key intermediate **9** started from L-arabinose and is outlined in Scheme 2. The known aldehyde **11** was prepared from L-arabinose in three steps according to the reported procedure.[5] Wittig reaction[6] of the aldehyde **11** with triphenylphosphonium methylidene followed by selective hydrolysis[7] of the terminal acetonide with 75% aqueous acetic acid afforded the 1,2-diol **13**. Regioselective monotosylation[8] of **13** followed by base treatment gave the epoxide **9** in 78% yield for two steps.[9]

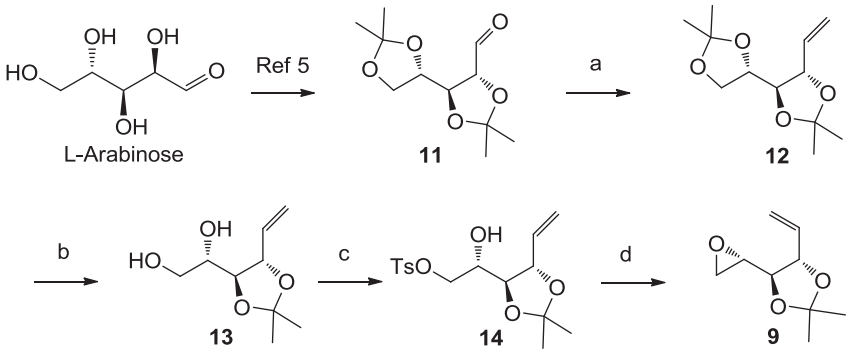
The known homoallylic alcohol **10** was prepared by treating commercially available (*S*)-(−)-propylene oxide with vinylmagnesium bromide in the presence of CuI.[10] Exposure the mixture of the epoxide **9** and the homoallyl alcohol **10** in 1:1.5 ratio to Grubbs second generation catalyst in dry DCM under reflux provided the desired (*E*)-alkene in 85% yield along with small amounts of the dimer of **10**.[11] The ring opening of the epoxide **8** with lithium acetylide from TMS−acetylene in the presence of $BF_3 \cdot Et_2O$ gave the corresponding homopropargylic alcohol **15** in 78% yield.[12] After deprotection of the TMS group in **15** with K_2CO_3 in methanol, the resulting terminal alkyne was treated with NBS (*N*-bromosuccinimide) in the presence of silver nitrate to afford the 1-bromoalkyne **17** in almost quantitative yield.[13] According to the Guibe's protocol, Pd-catalyzed hydrostannylation of the bromoalkyne **17** smoothly yielded the desired (*E*)-vinyl stannane **6** at room temperature (Scheme 3).[14]

Stille cross-coupling of **6** and the known aryl triflate **7**[15] proceeded smoothly to give the alkene **5** in 81% yield.[16] Hydrolysis of **5** with LiOH in a solution of THF/H_2O (2:1) afforded an almost quantitative yield of the free acid **18** (Scheme 4).

However, difficulties were encountered during the attempted macrocyclization of the resulting carboxylic acid to the corresponding macrolide. The Yamaguchi macrolactonization strategy[17] was first explored. Unfortunately, only a trace amount of cochliomycin A was obtained under this condition. Attempts to improve the yield by changing reaction concentration or going to higher temperature were fruitless. The Corey−Nicolaou double activation strategy[18] was also examined and no desired product was observed. Because of the failure of the original strategy for constructing macrolide from free acid **18**, a backup approach was adopted. Finally, according to De Brabander's conditions,[19] one-pot intramolecular lactonization was achieved with excess NaH in dry DMF, leading to cochliomycin A (**1**) in reasonable yield (Scheme 4). All the spectroscopic data and specific rotation data of our synthetic cochliomycin A are in good agreement with those reported values for natural product {$[\alpha]_D^{24}$ +10.5 (*c* 0.6, MeOH); Ref. 3: $[\alpha]_D^{30}$ +10.6 (*c* 0.5, MeOH); Ref. 2: $[\alpha]_D^{24}$ +10.5 (*c* 0.43, MeOH)}.

3. Conclusions

In conclusion, a convergent and stereoselective synthesis of the resorcylic acid lactone, cochliomycin A, has been achieved starting from readily available chiral pool L-arabinose. The key reactions involved olefin cross-metathesis, Stille cross-coupling and sodium hydride promoted one-pot intramolecular lactonization. Further synthetic studies on other cochliomycins and their biological evaluation are currently under investigation in our laboratory.



Scheme 2. Reagents and conditions: (a) CH_3PPh_3Br, *t*-BuOK, dry THF, rt, overnight; (b) 75% AcOH, rt, overnight, 77% (for two steps); (c) *p*-toluenesulfonyl chloride, dibutyltin oxide, dry CH_2Cl_2, 0 °C to rt, 4 h; (d) K_2CO_3, MeOH, rt, 3 h, 78% (for two steps).

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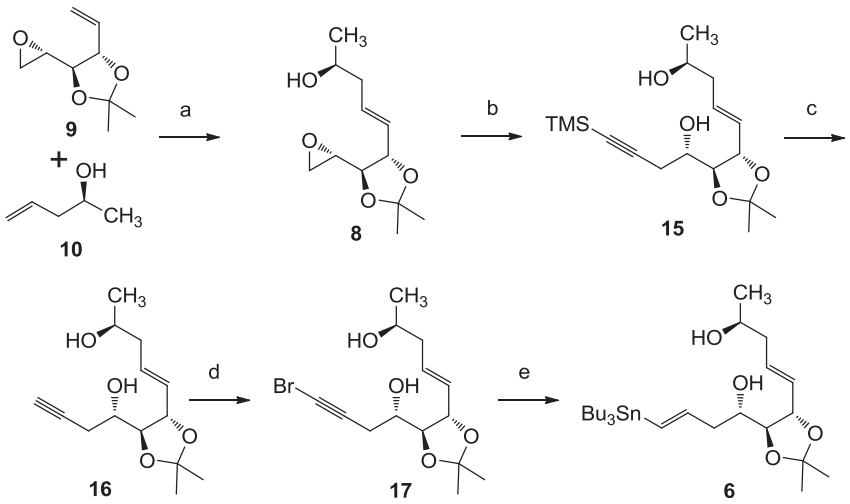
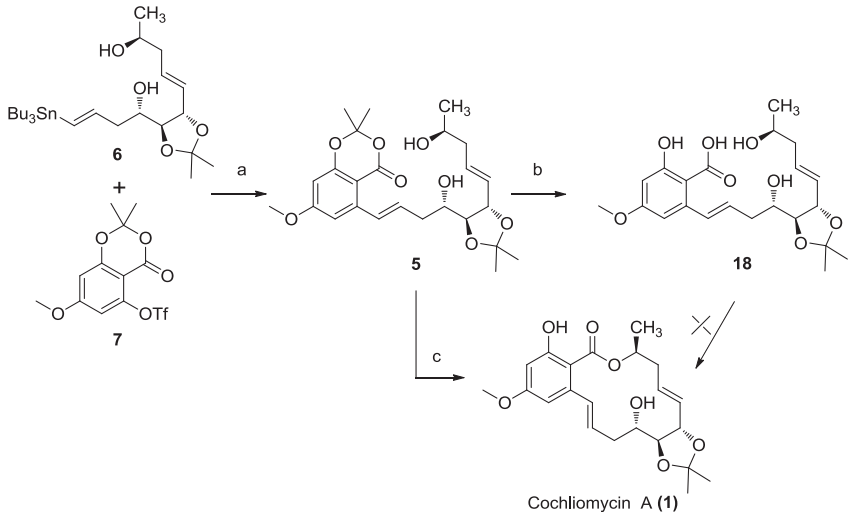


Scheme 3. Reagents and conditions: (a) Grubbs second generation catalyst, CH_2Cl_2, reflux, 24 h, 85%; (b) TMS–acetylene, *n*-BuLi, $BF_3{\cdot}Et_2O$, THF, −78 °C, 1 h, 78%; (c) K_2CO_3, MeOH, 12 h, 86%; (d) NBS, $AgNO_3$, acetone, 1 h, 97%; (e) $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt, 30 min, 85%.



Scheme 4. Reagents and conditions: (a) $Pd(dba)_2$, $AsPh_3$, LiCl, DMF, 60 °C, 2 h, 81%; (b) $LiOH{\cdot}H_2O$, THF/H_2O (2:1), 24 h. (c) NaH, dry DMF, 0 °C to rt, 1 h, 46%.

4. Experimental section

4.1. General

All anhydrous solvents were purified according to standard methods. All commercially available reagents were used without further purification. Reactions were monitored by thin-layer chromatography (TLC) on gel F_{254} plates. Flash chromatography (FC) was performed using silica gel (200–300 mesh) according to the standard protocol. Optical rotations were recorded in either a 5-cm microcell or a 2.5-cm microcell. High-resolution mass spectrometry data (HRMS) were acquired with a Q-TOF analyzer. ^1H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz (100 MHz for ^{13}C) NMR spectrometer.

*4.1.1. (4R,4′S,5S)-2,2,2′,2′-Tetramethyl-5-vinyl-4, 4′-bi(1,3-dioxolane) (**12**).* To a stirred suspension of methyl triphenylphosphonium bromide (131 g, 367 mmol) in anhydrous THF (300 mL) was added potassium *tert*-butoxide (45.5 g, 405 mmol) at 0 °C under N_2 atmosphere. The reaction mixture was stirred at 0 °C for 20 min and then at room temperature for 1 h. After the mixture was allowed to cool to 0 °C, a solution of **11** (29.6 g, 129 mmol) in anhydrous THF (50 mL) was added and the mixture was stirred at room temperature overnight. To this mixture was carefully added water (200 mL) and the mixture was extracted with ethyl acetate (800 mL), dried, filtered, and concentrated under reduced pressure to give a yellow syrup. This syrup was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:20) to give **12** with the contamination of triphenylphosphine oxide, which was used for next reaction without further purification; ^1H NMR (400 MHz, $CDCl_3$): δ 5.91 (ddd, J=6.0, 10.4, 16.8 Hz, 1H), 5.41 (d, J=17.2 Hz, 1H), 5.21 (d, J=10.4 Hz, 1H), 4.36 (td, J=1.2, 6.4 Hz, 1H), 4.07–4.15 (m, 2H), 3.93–3.96 (m, 1H), 3.70 (t, J=7.2 Hz, 1H), 1.41 (s, 6H), 1.40 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 136.3, 117.5, 110.0, 109.8, 81.5, 80.8, 67.4, 27.3, 27.3, 27.0, 25.6; ESI-HRMS calcd for $C_{12}H_{20}O_4$ ($[M+Na]^+$) 251.1253, found 251.1237.

*4.1.2. (S)-1-((4S,5S)-2,2-Dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethane-1,2-diol (**13**).* Compound **12** was added to 75% acetic acid (200 mL) and the mixture was stirred at room temperature overnight. The reaction mixture was azeotroped with toluene under reduced pressure below 30 °C to give a yellow syrup. This syrup was purified

by silica gel column chromatography (ethyl acetate/petroleum ether 1:1) to give **13** (18.6 g, 77% from **11**) as a colorless oil; $[\alpha]_D^{30}$ −65.4 (*c* 0.7, $CHCl_3$); IR (*ν*): 3308, 2986, 1372, 1225, 1168, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.89 (ddd, *J*=6.8, 10.0, 16.8 Hz, 1H), 5.43 (d, *J*=16.8 Hz, 1H), 5.26 (d, *J*=10.4 Hz, 1H), 4.41 (td, *J*=0.8, 7.2 Hz, 1H), 3.85–3.88 (m, 1H), 3.79 (dd, *J*=5.2, 8.0 Hz, 1H), 3.67–3.75 (m, 2H), 2.25 (br, 2H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 136.3, 118.7, 109.7, 81.3, 79.7, 72.5, 63.8, 27.2, 27.2; ESI-HRMS calcd for $C_9H_{16}O_4$ ($[M+Na]^+$) 211.0940, found 211.0917.

*4.1.3. (4R,5S)-2,2-Dimethyl-4-((S)-oxiran-2-yl)-5-vinyl-1, 3-dioxolane (**9**).* To a stirred solution of **13** (4 g, 21.3 mmol), Bu_2SnO (106 mg, 0.43 mmol), and triethylamine (2.967 mL, 21.3 mmol) in dry CH_2Cl_2, *p*-toluenesulfonyl chloride (4.07 g, 21.3 mmol) was added at 0 °C under N_2 atmosphere. The resulting solution was stirred for 4 h at room temperature. Water was added and the reaction mixture was extracted with CH_2Cl_2. The organic extract was washed with brine, dried, and concentrated under reduced pressure to afford the crude tosylate **14** as a colorless oil, which was used for next step without any purification. To a stirred solution of **14** in MeOH (50 mL), anhydrous K_2CO_3 (8.83 g, 64.0 mmol) was added under N_2 atmosphere. The resulting solution was stirred for 3 h at room temperature and filtered. The residue was washed with CH_2Cl_2, and the combined filtrates were concentrated under reduced pressure below 30 °C. The residue was redissolved in CH_2Cl_2, washed with brine, dried, and concentrated to give the crude product, which was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:40) to give **9** (2.82 g, 78% from **13**) as a colorless oil; $[\alpha]_D^{30}$ 25.1 (*c* 1.3, $CHCl_3$); IR (*ν*): 2957, 2926, 1653, 1373, 1259, 1218, 1176, 1062, 870 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.86 (ddd, *J*=6.8, 10.4, 17.2 Hz, 1H), 5.42 (dd, *J*=0.8, 17.2 Hz, 1H), 5.27 (dd, *J*=0.8, 10.4 Hz, 1H), 4.35 (t, *J*=7.2 Hz, 1H), 3.59 (dd, *J*=5.2, 8.0 Hz, 1H), 3.06–3.09 (m, 1H), 2.81 (dd, *J*=4.4, 5.2 Hz, 1H), 2.69 (dd, *J*=2.8, 4.8 Hz, 1H), 1.43 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 135.3, 119.2, 110.1, 80.6, 80.4, 51.5, 45.0, 27.2, 27.0; ESI-HRMS calcd for $C_9H_{14}O_3$ ($[M+Na]^+$) 193.0835, found 193.0829.

*4.1.4. (S,E)-5-((4S,5R)-2,2-Dimethyl-5-((S)-oxiran-2-yl)-1,3-dioxolan-4-yl)pent-4-en-2-ol (**8**).* To a stirred solution of **9** (1.17 g, 6.9 mmol) and **10** (885 mg, 10.3 mmol) in dry CH_2Cl_2 (2 mL), 2% mol of Grubbs second generation catalyst was added under N_2 atmosphere. The reaction mixture was stirred for 24 h under reflux. The reaction mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:6) to give **8** (1.33 g, 85%) as a colorless oil; $[\alpha]_D^{30}$ 64.7 (*c* 1.3, $CHCl_3$); IR (*ν*): 3433, 2985, 2921, 1597, 1454, 1376, 1219, 1160, 1112, 1058 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.85–5.93 (m, 1H), 5.56–5.62 (m, 1H), 4.37 (t, *J*=8.0 Hz, 1H), 3.83–3.91 (m, 1H), 3.51 (dd, *J*=5.6, 8.4 Hz, 1H), 3.06 (ddd, *J*=2.4, 3.6, 6.4 Hz, 1H), 2.82 (dd, *J*=4.0, 4.8 Hz, 1H), 2.70 (dd, *J*=2.4, 4.8 Hz, 1H), 2.23–2.25 (m, 2H), 1.67 (br, 1H), 1.44 (s, 3H), 1.43 (s, 3H), 1.21 (d, *J*=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.8, 129.8, 109.8, 80.3, 80.2, 67.2, 51.3, 44.9, 42.2, 27.1, 26.8, 23.0; ESI-HRMS calcd for $C_{12}H_{20}O_4$ ($[M+Na]^+$) 251.1253, found 251.1264.

*4.1.5. (S,E)-5-((4S,5S)-5-((S)-1-Hydroxy-4-(trimethylsilyl)but-3-yn-1-yl)-2, 2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (**15**).* To a stirred solution of trimethylsilylacetylene (1.24 mL, 8.76 mmol) in anhydrous THF (20 mL), was added *n*-BuLi (1.6 M in hexanes, 5.34 mL, 8.54 mmol) dropwise at −78 °C under N_2 atmosphere. The resulting solution was slowly warmed to 0 °C and stirred at this temperature for 1 h. The reaction mixture was then cooled to −78 °C and $BF_3{\cdot}Et_2O$ (0.60 mL, 4.82 mmol) was added dropwise. After 20 min at −78 °C, a solution of **8** (500 mg, 2.19 mmol) in THF (20 mL) was added via cannula. After 1 h of stirring at this temperature, the reaction mixture was hydrolyzed by adding brine (30 mL). The aqueous phase was extracted with ethyl acetate (3×50 mL) and the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:4) to give **15** (554 mg, 78%) as a colorless oil; $[\alpha]_D^{30}$ 50 (*c* 0.6, $CHCl_3$); IR (*ν*): 3415, 2985, 2964, 2932, 2901, 2177, 1372, 1250, 1064 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.84–5.92 (m, 1H), 5.63 (dd, *J*=8.0, 15.6 Hz, 1H), 4.43 (t, *J*=8.0 Hz, 1H), 3.85–3.95 (m, 2H), 3.80 (dd, *J*=5.6, 8.0 Hz, 1H), 2.51 (dd, *J*=1.6, 6.8 Hz, 2H), 2.22–2.26 (m, 2H), 1.95 (br, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.20 (d, *J*=6.0 Hz, 3H), 0.156 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.1, 131.0, 108.9, 102.4, 87.6, 81.7, 78.7, 69.8, 67.0, 42.0, 27.0, 26.9, 25.0, 22.8, 0.0; ESI-HRMS calcd for $C_{17}H_{30}O_4Si$ ($[M+Na]^+$) 349.1805, found 349.1815.

*4.1.6. (S,E)-5-((4S,5S)-5-((S)-1-Hydroxybut-3-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (**16**).* To a solution of **15** (397 mg, 1.22 mmol) in MeOH (10 mL), was added K_2CO_3 (252 mg, 1.83 mmol). The mixture was stirred for 12 h at room temperature before water (5 mL) was added. The mixture was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, filtered, and concentrated. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:3) to give **16** (268 mg, 86%) as a colorless oil; $[\alpha]_D^{30}$ 45 (*c* 0.6, $CHCl_3$); IR (*ν*): 3301, 2964, 2924, 2856, 2119, 1670, 1374, 1062 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.83–5.92 (m, 1H), 5.65 (dd, *J*=7.6, 15.6 Hz, 1H), 4.43 (t, *J*=7.6 Hz, 1H), 3.92–3.96 (m, 1H), 3.86–3.90 (m, 1H), 3.81 (dd, *J*=5.2, 7.6 Hz, 1H), 2.48–2.51 (m, 2H), 2.18–2.31 (m, 2H), 2.07 (t, *J*=2.8 Hz, 1H), 1.69 (br, 2H), 1.42 (s, 3H), 1.41 (s, 3H), 1.20 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.0, 131.7, 109.4, 81.9, 80.2, 79.1, 71.6, 70.3, 67.4, 42.3, 27.4, 27.3, 23.9, 23.2; ESI-HRMS calcd for $C_{14}H_{22}O_4$ ($[M+Na]^+$) 277.1444, found 277.1412.

*4.1.7. (S,E)-5-((4S,5S)-5-((S)-4-Bromo-1-hydroxybut-3-ynyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pent-4-en-2-ol (**17**).* To a solution of **16** (218 mg, 0.86 mmol) in acetone (25 mL), was added silver nitrate (44 mg, 0.26 mmol) and *N*-bromosuccinimide (183 mg, 1.03 mmol). The reaction mixture was stirred for 1 h, poured into saturated $NaHCO_3$ (5 mL) and saturated sodium thiosulfate (5 mL), and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:3) to give **17** (278 mg, 97%) as a colorless oil; $[\alpha]_D^{30}$ 73.8 (*c* 0.9, $CHCl_3$); IR (*ν*): 3374, 2960, 2921, 2853, 2309, 1603, 1376, 1123, 1059 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.84–5.91 (m, 1H), 5.62 (dd, *J*=8.0, 15.6 Hz, 1H), 4.41 (t, *J*=8.0 Hz, 1H), 3.85–3.94 (m, 2H), 3.77 (dd, *J*=5.6, 8.0 Hz, 1H), 2.50 (d, *J*=6.4 Hz, 2H), 2.22–2.26 (m, 2H), 2.10 (br, 2H), 1.42 (s, 3H), 1.40 (s, 3H), 1.20 (d, *J*=6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 132.4, 131.5, 109.4, 81.9, 79.1, 76.3, 70.2, 67.5, 42.2, 41.3, 27.4, 27.3, 25.1, 23.2; ESI-HRMS calcd for $C_{14}H_{21}BrO_4$ ($[M+Na]^+$) 355.0515, found 355.0514.

*4.1.8. (S,E)-5-((4S,5S)-5-((S,E)-1-Hydroxy-4-(tributylstannyl)but-3-enyl)-2,2-dimethyl-1, 3-dioxolan-4-yl)pent-4-en-2-ol (**6**).* To a solution of the alkynyl bromide **17** (256 mg, 0.77 mmol) in anhydrous THF (20 mL), was added $Cl_2Pd(PPh_3)_2$ (11 mg, 0.0154 mmol) and tributyltin hydride (0.42 mL, 1.54 mmol). The reaction mixture was stirred for 30 min, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:6) to give **6** (357 mg, 85%) as a colorless oil; $[\alpha]_D^{30}$ 28.8 (*c* 0.8, $CHCl_3$); IR (*ν*): 3411, 2957, 2926, 2870, 2850, 1673, 1597, 1457, 1376, 1244, 1165, 1056 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): *δ* 5.81–6.17 (m, 3H), 5.60 (dd, *J*=8.0, 15.6 Hz, 1H), 4.44 (t, *J*=8.0 Hz, 1H), 3.80–3.93 (m, 2H), 3.70 (dd, *J*=4.8, 8.0 Hz, 1H), 2.16–2.51 (m, 5H), 2.06–2.10 (m, 1H), 1.46–1.71 (m, 6H), 1.42 (s,

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3H), 1.41 (s, 3H), 1.25–1.36 (m, 6H), 1.20 (d, J=6.4 Hz, 3H), 0.79–0.96 (m, 15H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.4, 133.5, 132.0, 109.1, 82.8, 78.7, 70.7, 67.4, 42.4, 41.9, 29.5, 27.6, 27.4, 27.3, 23.2, 14.1, 9.8; ESI-HRMS calcd for $C_{26}H_{50}O_4Sn$ ([M+Na]$^+$) 569.2628, found 569.2628.

*4.1.9. 5-((S,E)-4-Hydroxy-4-((4S,5S)-5-((S,E)-4-hydroxypent-1-en-1-yl)-2,2-dimethyl-1, 3-dioxolan-4-yl)but-1-en-1-yl)-7-methoxy-2,2-dimethyl-4H-benzo[d][1,3]dioxin-4-one (**5**).* To a flame-dried flask containing triflate **7** (107 mg, 0.301 mmol), $Pd(dba)_2$ (106 mg, 0.184 mmol), $AsPh_3$ (56 mg, 0.183 mmol), and LiCl (29 mg, 0.684 mmol), was added anhydrous DMF 3 mL under N_2 atmosphere. The resulting mixture was stirred at room temperature for 30 min before addition of vinyl stannane **6** (126 mg, 0.231 mmol). The reaction was heated to 60 °C for 2 h, cooled to room temperature, and then concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:1) to give **5** (86 mg, 81%) as a colorless oil; $[\alpha]_D^{30}$ 16.7 (c 0.6, $CHCl_3$); IR (ν): 3372, 2923, 1726, 1659, 1603, 1460, 1429, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J=16.0 Hz, 1H), 6.69 (d, J=2.4 Hz, 1H), 6.34 (d, J=2.4 Hz, 1H), 6.09–6.16 (m, 1H), 5.85–5.92 (m, 1H), 5.63 (dd, J=7.6, 15.2 Hz, 1H), 4.47 (t, J=7.6 Hz, 1H), 3.83–3.93 (m, 5H), 3.73 (dd, J=5.2, 8.0 Hz, 1H), 2.34–2.56 (m, 3H), 2.10–2.28 (m, 3H), 1.69 (s, 6H), 1.41 (s, 6H), 1.18 (d, J=6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 160.7, 159.0, 144.1, 132.2, 132.2, 131.7, 130.3, 109.1, 109.0, 105.5, 104.0, 100.7, 82.8, 79.1, 71.4, 67.5, 56.0, 42.3, 37.0, 27.4, 27.3, 25.9, 23.2; ESI-HRMS calcd for $C_{25}H_{34}O_8$ ([M+Na]$^+$) 485.2145, found 485.2130.

*4.1.10. Cochliomycin A (**1**).* To a stirred solution of **5** (57 mg, 0.123 mmol) in anhydrous DMF (10 mL), was added sodium hydride (86 mg, 2.15 mmol, 60% oil dispersion) at 0 °C under N_2 atmosphere. The mixture was stirred for 1 h. To this mixture was added saturated aqueous NH_4Cl and the mixture was extracted with ethyl acetate, dried, filtered, and concentrated under reduced pressure. This residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:3) to give **1** (23 mg, 46%) as a white solid (mp 68 °C); $[\alpha]_D^{24}$ 10.5 (c 0.6, MeOH); IR (ν): 3405, 2921, 2372, 2307, 1629, 1378 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.49 (s, 1H), 7.17 (dd, J=2.0, 15.2 Hz, 1H), 6.48 (d, J=2.8 Hz, 1H), 6.40 (d, J=2.8 Hz, 1H), 6.00 (ddd, J=5.2, 8.0, 15.2 Hz, 1H), 5.73 (ddd, J=2.8, 10.4, 15.2 Hz, 1H), 5.53 (dd, J=8.8, 15.2 Hz, 1H), 5.42–5.48 (m, 1H), 4.57 (t, J=8.4 Hz, 1H), 4.21 (ddd, J=2.0, 4.8, 12.0 Hz, 1H), 3.90 (dd, J=2.4, 8.0 Hz, 1H), 3.82 (s, 3H), 2.73–2.80 (m, 1H), 2.18–2.55 (m, 4H), 1.45 (d, J=6.4 Hz, 3H), 1.44 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.8, 164.8, 164.0, 142.1, 134.1, 132.7, 129.5, 126.4, 108.5, 107.2, 104.4, 100.1, 81.4, 75.3, 70.6, 68.8, 55.4, 37.9, 36.0, 27.0, 27.0, 19.2; ESI-HRMS calcd for $C_{22}H_{28}O_7$ ([M+Na]$^+$) 427.1727, found 427.1728.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.03.001.

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