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Asymmetric Total Syntheses of Cochliomycin A and Zeaenol

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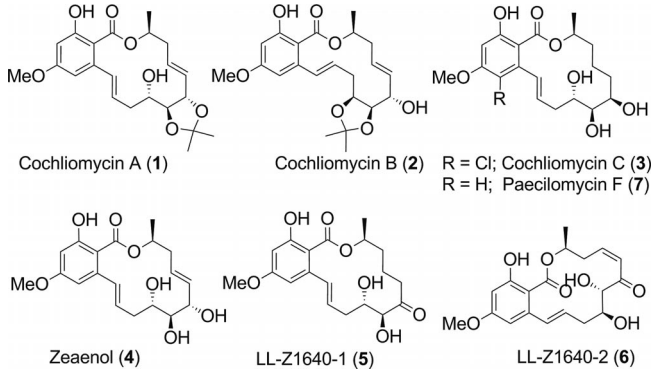
The first asymmetric total syntheses of two resorcylic acid lactones (RALs) – cochliomycin A and zeaenol – have been achieved in a divergent way. The main highlight of our strategy involves successful application of stereoselecive Keck allylation and Julia–Kocienski olefination to access an advanced intermediate, by starting from L-tartaric acid as a chiral pool compound. This intermediate is coupled with a trisubstituted benzoic acid to afford a common RCM precursor for both target molecules. Ring-closing metathesis at a late stage, followed by functional group manipulation, yielded the target molecules in an efficient way.

Introduction

Resorcylic acid lactones (RALs) have been known for decades, with the first isolation of radicicol (monorden) in 1953,[1] followed by zearalenone in 1962,[2] LL-Z1640-2 in 1978,[3] and hypothemycin in 1980.[4] After that a series of 14-membered resorcylic acid lactones, such as radicicol A,[5] aigialomycins A–E,[6] pochonins A–P,[7] and paecilomycins A–F,[8] were reported as fungal polyketide metabolites. All of these compounds have received considerable attention, due to their potent biological properties, which include antifungal,[9] cytotoxic,[6,10] antimalarial,[10] antiviral, antiparasitic,[4,11] estrogenic,[12] nematicidal,[13] protein tyrosine kinase, and ATPase inhibition activities.[14]

Recently two new 14-membered resorcylic acid lactones each containing a rare natural acetonide group [cochliomycins A and B (**1** and **2**, Scheme 1)] and one new 5-chloro-substituted lactone [cochliomycin C (**3**)], together with four known analogues – namely, zeaenol (**4**),[15] LL-Z1640-1 (**5**),[3] LL-Z1640-2 (**6**),[3] and paecilomycin F (**7**)[8] – were obtained from the fungus *Cochliobolus lunatus* in the South China Sea.[16] These lactones were evaluated against the larval settlement of the barnacle *Balanus amphitrite*, and antifouling activity was detected for the first time in this type of metabolites.

The frameworks of cochliomycin A (**1**) and zeaenol (**4**) are basically similar except for the acetonide linkage in **1** (Scheme 1). The diverse biological functions and curious skeletal features of these lactones tempted us to synthesize them. There are numerous reports containing total syntheses of RALs,[17] but to the best of our knowledge no syntheses of the two target molecules cochliomycin A and zeaenol have been reported to date. One of the finest synthetic strategies reported for RALs involves a biomimetic synthesis featuring a late-stage aromatization of suitably substituted triketo esters, as demonstrated by Barett et al. in their total synthesis.[17a,17b]



Scheme 1. Structures of some recently isolated RALs.

Present Work

Scheme 2 outlines our retrosynthetic analysis of cochliomycin A (**1**) and zeaenol (**4**). We planned to adopt ring-closing metathesis (RCM) at a late stage of the synthesis to construct the 14-membered macrocyclic core. It was imagined that the RCM precursor should be accessible through a Mitsunobu esterification between secondary aliphatic alcohol **9** and trisubstituted benzoic acid **8** and that the aromatic acid **8** should be obtainable from 3,5-dihydroxybenzoic acid through formylation of a styrene-type compound, whereas it was intended to synthesize the other chiral alcohol intermediate **9** from L-tartaric acid through asymmetric Keck allylation and Julia–Kocienski-type olefination with sulfone **11**. It was envisaged that the

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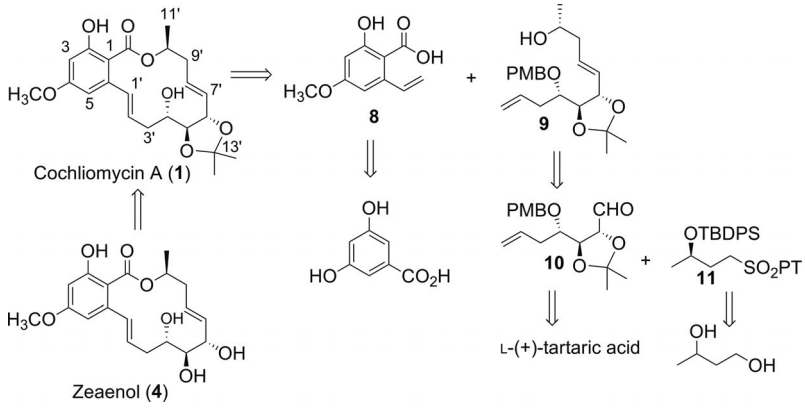


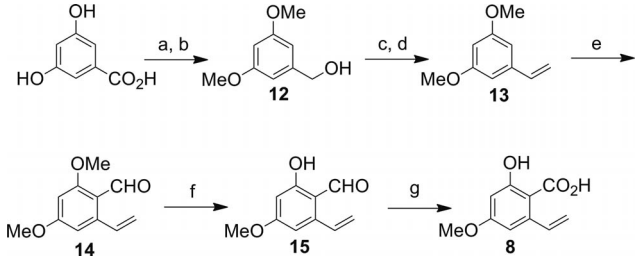
Scheme 2. Retrosynthetic analysis of cochliomycin A and zeaenol.

stereocenter in the sulfone **11** could be established by application of a metal/enzyme combined DKR (dynamic kinetic resolution) strategy to racemic butane-1,3-diol.

Results and Discussion

Synthesis of Aromatic Acid 8

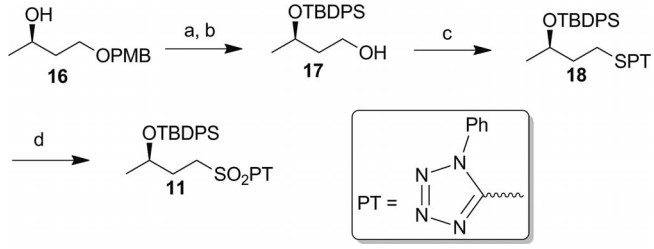
Trisubstituted benzoic acid **8**, with a pendant vinyl group, was synthesized from 3,5-dihydroxybenzoic acid in seven steps (Scheme 3). The synthetic sequence started with trimethylation of 3,5-dihydroxybenzoic acid with dimethylsulfate and K_2CO_3 as a base, followed by reduction of the ester functionality with LAH in dry ether at 0 °C to give 3,5-dimethoxybenzyl alcohol (**12**, 94% yield in two steps). PCC oxidation of the benzyl alcohol functionality and subsequent one-carbon extension by Wittig olifination produced the substituted styrene **13** in 81.6% yield (two steps). Vilsmeier–Haack formylation ($POCl_3$ in DMF) of compound **13** at –5 °C to room temperature for 8 h regiospecifically introduced the aldehyde group in the position *ortho* to the vinyl group to furnish compound **14** in 87% yield. Selective demethylation with BBr_3 afforded the aldehyde **15** in 92% isolated yield.[18] Finally, oxidation under Pinnick conditions[19] provided the required benzoic acid derivative **8** in good yield (90% based on recovered aldehyde, overall yield 54% from 3,5-dihydroxybenzoic acid).



Scheme 3. Reagents and conditions: (a) Me_2SO_4 (3.5 equiv.), K_2CO_3, acetone, reflux, 4 h 96%; (b) LAH, 0 °C, 1 h, 98%; (c) PCC, DCM, 2 h, 85%; (d) $Ph_3PCH_3^+I^-$, KO*t*Bu, THF,0 °C to r.t. 96%; (e) $POCl_3$, DMF, 0 °C to r.t., 8 h, 87%; (f) BBr_3, DCM, 0 °C, 1 h, 92%; (g) $NaClO_2$, Na_2HPO_4, 2-methylbut-2-ene, *t*BuOH/H_2O (1:1), 3 h, 60% (based on 30% recovered aldehyde).

Synthesis of Sulfone 11

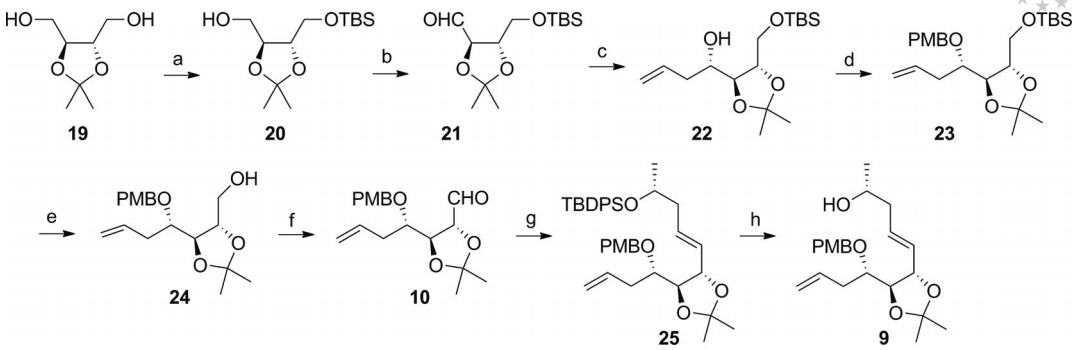
The sulfone intermediate was synthesized by starting from the known alcohol (*R*)-**16** (Scheme 4), previously prepared in our group[20d] by a metal/enzyme combined DKR strategy.[20] The secondary hydroxy group in **16** was protected as a TBDPS (*tert*-butyldiphenylsilyl) ether by treatment with imidazole/TBDPSCl, and removal of the PMB group was successfully achieved with DDQ[21] to yield compound **17** in 82% yield (two steps). Finally, the primary hydroxy group was transformed into the corresponding 1-phenyl-1*H*-tetrazol-5-yl sulfide **18** through a Mitsunobu reaction, and subsequent Mo^{IV}-catalyzed oxidation[22] of **18** afforded the desired sulfone **11** in 88% yield over two steps.



Scheme 4. Reagents and conditions: (a) imidazole, TBDPSCl, 95%; (b) DDQ, DCM/H_2O (19:1), 86%; (c) PTSH, PPh_3, DIAD, THF; (d) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, (88% in two steps).

Synthesis of Alcohol 9

Synthesis of the alcohol fragment **9** began with the preparation of aldehyde **10** (Scheme 5) in seven steps from the known C_2-symmetric diol **19**. Monosilylation of 2,3-di-*O*-isopropylidene-L-threitol (**19**) with TBSCl in THF in the presence of NaH by McDougal's protocol[23] afforded the mono-TBS-protected acetonide **20** in 85% yield. Oxidation of the free primary hydroxy group of **20** under Swern conditions[24] afforded aldehyde **21** in excellent yield (90%). Aldehyde **21** was then subjected to Keck asymmetric allylation[25] to produce the allylic alcohol **22** in 78% yield with a 19:1 diastereomeric ratio. Protection of the free hydroxy group as a PMB ether (compound **23**) was achieved by treating compound **22** with NaH, PMBBr, and TBAI (tetra-



Scheme 5. Reagents and conditions: (a) TBSCl (1 equiv.), NaH, THF, r.t., 1 h, 85%; (b) $(COCl)_2$, Me_2SO, Et_3N, –78 °C, 90%; (c) allyltributyltin, $Ti(OPr)_4$, (*S*)-BINOL, toluene, –78 °C then –15 °C, 72 h, 78%; (d) PMBBr, NaH, THF, r.t., 88%; (e) TBAF, THF, r.t., 2 h, 92%; (f) DMP, $NaHCO_3$, DCM, r.t., 1.5 h, 94%; (g) **11**, KHMDS, 18-c-6, THF, –78 °C, 0.5 h, 75%; (h) TBAF, THF, r.t., 24 h, 88%.

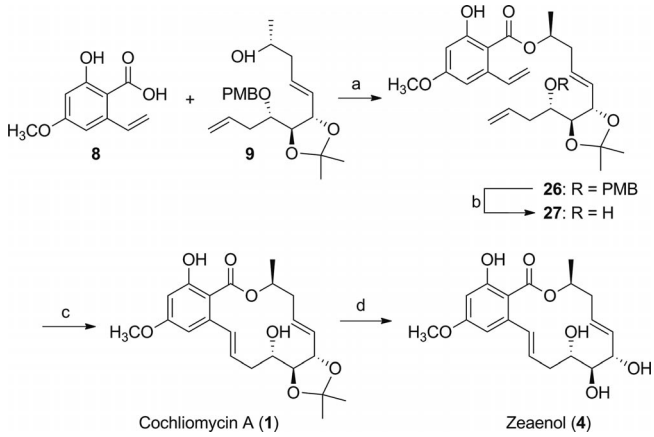
n-butylammonium iodide). Removal of the TBS group with TBAF afforded primary alcohol **24** in 81% yield (in two steps). Dess–Martin periodinane oxidation of alcohol **24** in the presence of $NaHCO_3$ produced intermediate aldehyde **10** in 94% yield.[26]

Now that both aldehyde **10** and sulfone **11** were available in enantiomerically pure forms, we tried Julia–Kocienski olefination under several conditions. With LHMDS as a base the reaction gave the desired olefin **25** in poor yield. On the other hand, a good yield was achieved when KHMDS was used as a base, but the obtained *E*/*Z* selectivity was not so desirable (*E*/*Z* = 2:1). The low selectivity obtained seemed to be generated by some chelation effects of oxygen functional groups (OTBDPS) in the sulfone **11** and the aldehyde **10** with potassium cation, so we tried other conditions with employment of external additives to stop this chelation. When 18-crown-6 was added, *trans* olefin **25** was successfully obtained in good yield and with high selectivity (75%, *E*/*Z* = 20:1). It had already been demonstrated that the counterion of the applied base and the polarities of the solvents exhibit a strong influence on the stereochemical outcomes of reactions between aliphatic PT sulfones and aliphatic aldehydes.[27] The effects of this additive on the stereochemistry of the olefin **25** were remarkable and superior to those observed with HMPA as a cation chelator (*E*/*Z* 4:1). Careful removal of the secondary TBDPS ether of olefin **25** with TBAF in room temperature afforded the alcohol **9** in 88% yield (Scheme 5).

Completion of the Synthesis

With the vinyl-substituted benzoic acid **8** and suitably functionalized alcohol **9** to hand, the esterification reaction between the two fragments under Mitsunobu conditions[28] proceeded cleanly to generate ester **26** (Scheme 6) in 85% yield. To complete the total synthesis, macrocyclization and deprotection were required. Before ring closure the PMB group was removed by treatment with DDQ, because it was potentially problematic in RCM as documented earlier.[20d] Finally, compound **27**, with two terminal olefins, furnished the target molecule cochliomycin A (**1**) in 72% yield upon treatment with the second-generation Grubbs catalyst.[29]

Removal of the acetonide functionality in compound **1** was achieved by treatment with HCl (2 N) to afford the other target molecule – zeaenol (**4**) – in 92% yield. The analytical data (^1H, ^{13}C NMR and optical rotation values) for both compounds are consistent with those of the natural products.



Scheme 6. Reagents and conditions: (a) DIAD, PPh_3, toluene, 1.5 h, 85%; (b) DDQ, DCM/H_2O (19:1), 86%; c) 2nd-generation Grubbs catalyst, DCM, 40 °C, 6 h, 72%; (d) HCl (2 N), THF, 20 h, 92%.

Conclusions

In conclusion, we have synthesized two RALs – cochliomycin A and zeaenol – for the first time, from the cheap commercially available starting materials 3,5-dihydroxybenzoic acid and L-(+)-tartaric acid, in 6.5% and 6% overall yields, respectively. Highlights of our synthetic venture included effective Keck asymmetric allylation on a acetonide-protected aldehyde, an advantageous *E*-selective Julia–Kocienski olefination on a highly elaborate substrate, and a late-stage RCM reaction. Synthetic studies directed towards several structurally related RALs (cochliomycins B and C, paecilomycin F) are still under investigation in our laboratory.

Experimental Section

General Information: Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification. THF and diethyl ether were distilled from sodium benzophenone ketyl. Dimethylformamide (DMF) and dimethylsulfoxide (DMSO) were distilled from calcium hydride. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm silica gel plates (Merck) with UV light, ethanolic anisaldehyde, and phosphomolybdic acid/heat as developing agents. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded with Bruker 200 and 400 MHz spectrometers at 25 °C in $CDCl_3$ with TMS as the internal standard. ^{13}C NMR spectra were recorded in a complete proton decoupling environment. The chemical shift values are listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Optical rotations were measured with a JASCO P1020 digital polarimeter. IR spectra were recorded with a Perkin–Elmer Rx1 instrument. Mass spectral analysis was performed at IICT, Hyderabad, India.

Methyl 3,5-Dimethoxybenzoate: Dimethyl sulfate (22 mL, 228 mmol, 3.5 equiv.) was added at room temperature to a mechanically stirred suspension of 3,5-dihydroxybenzoic acid (10 g, 65 mmol) and K_2CO_3 (36 g, 260 mmol, 4 equiv.) in acetone (100 mL). The reaction mixture was vigorously stirred at reflux for 4 h, then allowed to cool to room temperature and filtered. The filter solid was rinsed with acetone (2 × 100 mL) and most of the acetone was removed with a rotary evaporator. The residue was diluted with NH_4OH solution (5%, 50 mL), stirred for 5 min, and extracted with Et_2O (100 + 2 × 50 mL). The Et_2O solution was washed with HCl (5%) and then with saturated $NaHCO_3$ solution, dried with Na_2SO_4, and filtered, and the solvents were evaporated to dryness (10 mbar) with a rotary evaporator. The crude product was dissolved in hot MeOH (20 mL), and the solution was allowed to cool to 23 °C, followed by slow dropwise addition of deionized water (10 mL) to induce crystallization. The crystals were filtered through a sintered frit, rinsed on the filter with a cooled (4 °C) mixture of deionized water/methanol, and dried under vacuum to remove all water to afford the methyl ester (yield = 96%) as a white powder, m.p. 42 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 7.2 (s, 2 H), 6.65 (s, 1 H), 3.9 (s, 3 H), 3.82 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 166.9, 160.7, 132.1, 107.2, 105.8, 55.6, 52.4 ppm.

(3,5-Dimethoxyphenyl)methanol (12): Methyl 3,5-dimethoxybenzoate (4 g, 20.4 mmol) was added at 0 °C to a stirred suspension of LAH (775 mg, 20.4 mmol) in dry ether (80 mL). The mixture was stirred at 0 °C for 1 h and the reaction mixture was then carefully quenched with saturated Na_2SO_4 solution. It was then filtered and the solid was extracted with hot diethyl ether and concentrated in vacuo to give almost pure (3,5-dimethoxyphenyl)methanol as a colorless oil, which crystallized when stored, yield 3.36 g (99%), m.p. 47–47.5 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.50 (s, 2 H), 6.36 (s, 1 H), 4.6 (s, 2 H), 3.77 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.0, 143.5, 104.6, 99.7, 65.2, 55.4 ppm. IR: $\tilde{\nu}$ = 3420, 2940, 2064, 1609 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{12}O_3Na$ [M + Na]$^+$ 191.0684; found 191.0681.

3,5-Dimethoxybenzaldehyde: A solution of (3,5-dimethoxyphenyl)-methanol (**12**, 5 g, 29.7 mmol) in CH_2Cl_2 (20 mL) was added dropwise at room temperature to a stirred suspension of pyridinium chlorochromate (PCC, 9.35 g, 1.5 equiv.) in CH_2Cl_2 (80 mL). The mixture was stirred at room temperature for 24 h and then filtered through a pad of celite. The filter pad was washed with CH_2Cl_2 (2 × 30 mL). Most of the CH_2Cl_2 was removed under reduced pressure, and the residue was diluted with Et_2O (100 mL). The ether solution was washed twice with NaOH (5%), then with HCl (5%) and with saturated $NaHCO_3$ solution, and finally with brine, followed by drying with Na_2SO_4 and concentration in vacuo. The crude product was dissolved in a minimum amount of hot MeOH and recrystallized by slow addition of deionized water. The crystals were filtered, rinsed with a cold MeOH/H_2O mixture, and then dried under vacuum to remove all water; yield 4.2 g (81%) as colorless crystals, m.p. 46–47 °C. ^1H NMR (200 MHz, $CDCl_3$): δ = 9.8 (s, 1 H), 6.92 (s, 2 H), 6.61 (s, 1 H), 3.75 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 191.9, 161.3, 138.4, 115.4, 107.1, 55.6 ppm. IR: $\tilde{\nu}$ = 2942, 2842, 1696, 1598 cm^{-1}. HRMS (ESI): calcd. for $C_9H_{10}O_3Na$ [M + Na]$^+$ 189.0528; found 189.0534.

1,3-Dimethoxy-5-vinylbenzene (13): KO*t*Bu (5.6 g, 50 mmol, 2 equiv.) was added in one portion to a stirred suspension of methyltriphenylphosphonium iodide (21 g, 55 mmol, 2.2 equiv.) in dry diethyl ether (100 mL). The mixture was stirred for 2 h at room temperature and then cooled to 0 °C, followed by the addition of a solution of 3,5-dimethoxybenzaldehyde (4.15 g, 25 mmol) in dry ether (20 mL) at the same temperature. The cooling bath was removed and the mixture was allowed to come to room temperature. Next, the reaction was quenched by addition of dry MeOH (10 mL). The solvents were removed under reduced pressure and the residue was passed through a short pad (4 cm) of silica gel with petroleum ether/ethyl acetate 15:1 as eluent to give 3,5-dimethoxystyrene (3.94 g, 96%) as a colorless oil. ^1H NMR (200 MHz, $CDCl_3$): δ = 6.73–6.58 (m, 3 H), 6.42–6.40 (m, 1 H), 5.75 (dd, J = 17.4, 2.4 Hz, 1 H), 5.27 (dd, J = 17.4, 8.8 Hz, 1 H), 3.80 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 161.0, 139.7, 136.9, 114.4, 104.4, 100.1, 55.4 ppm. IR: $\tilde{\nu}$ = 2938, 2836, 1592, 1458 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{12}O_2Na$ [M + Na]$^+$ 187.0735; found 187.0729.

2,4-Dimethoxy-6-vinylbenzaldehyde (14): 1,3-Dimethoxy-5-vinylbenzene (**13**, 4.2 g, 25.6 mmol) was dissolved in anhydrous DMF (350 mL) and the mixture was cooled to 0 °C. $POCl_3$ (3.59 mL, 5.88 g, 38.4 mmol) was added dropwise over 5 min. The reaction mixture was stirred for 30 min at 0 °C and the cooling bath was removed. The reaction mixture was stirred for 8 h at room temperature, and water (300 mL) was added. The yellow mixture was extracted with CH_2Cl_2 (4 × 500 mL), dried ($MgSO_4$), and filtered through paper and the solvents were evaporated to dryness in vacuo. Silica gel column chromatography (ethyl acetate/petroleum ether 1:3) yielded the target aldehyde **14** in 87% yield as a white solid (when stored in a refrigerator). ^1H NMR (200 MHz, $CDCl_3$): δ = 10.46 (s, 1 H), 7.56 (dd, J = 17.2, 10.8 Hz, 1 H), 6.59 (d, J = 2.2 Hz, 1 H), 6.4 (d, J = 2.4 Hz, 1 H), 5.59 (dd, J = 17.2, 2.8 Hz, 1 H), 5.46 (dd, J = 10.8, 2.8 Hz, 1 H), 3.88 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 190.6, 164.8, 143.6, 136.6, 117.5, 116.4, 105.7, 104.6, 97.5, 56.1, 55.7 ppm. IR: $\tilde{\nu}$ = 2940, 2841, 1673, 1593 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{12}O_3Na$ [M + Na]$^+$ 215.0684; found 215.0688.

2-Hydroxy-4-methoxy-6-vinylbenzaldehyde (15): Aldehyde **14** (800 mg, 4.16 mmol) was dissolved in anhydrous CH_2Cl_2 (40 mL), and BBr_3 (8.3 mL, 1*M*, 8.3 mmol) was added over 5 min at 0 °C under N_2. The reaction mixture was stirred for 1 h at 0 °C, water (20 mL) was added, and the phases were separated. The aqueous phase was extracted with additional CH_2Cl_2 (2 × 50 mL), the combined organic extracts were dried (Na_2SO_4), and the solvents were evaporated to dryness in vacuo. The crude material was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:10) to give the target compound **15** (682 mg) as a white solid material in 92% yield. ^1H NMR (200 MHz, $CDCl_3$): δ = 12.34 (s, 1 H), 10.04 (s, 1 H), 7.19–7.04 (m, 1 H), 6.42 (d, J = 2.4 Hz, 1 H), 6.29 (d, J = 2.4 Hz, 1 H), 5.65–5.44 (m, 2 H), 3.8 (s, 3 H) ppm. ^{13}C

NMR (50 MHz, $CDCl_3$): δ = 193.2, 166.7, 166.1, 144.9, 132.1, 121.3, 112.3, 107.3, 100.1, 55.8 ppm. IR: $\tilde{\nu}$ = 3447, 2980, 2365, 1617 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{10}O_3Na$ $[M + Na]^+$ 201.0528; found 201.0533.

2-Hydroxy-4-methoxy-6-vinylbenzoic Acid (8): Aldehyde **15** (470 mg, 2.6 mmol) was dissolved in *t*BuOH (15 mL) and 2-methylbut-2-ene (8 mL, 2 M in THF). A solution of $NaClO_2$ (80% purity, 1433 mg, 15.8 mmol) and NaH_2PO_4 (936 mg, 7.8 mmol) in H_2O (15 mL) was added to this mixture. After 2 h, the yellow, biphasic reaction mixture was poured onto H_2O (15 mL) and EtOAc (30 mL). The mixture was acidified with HCl solution (1 M, ≈5 mL). The layers were separated. The organic solvent was dried, filtered, and concentrated in vacuo. The crude material was purified by flash column chromatography (ethyl acetate/petroleum ether 1:5) to give acid **8** (303 mg, 60%) as a solid. ^1H NMR (200 MHz, $CDCl_3$): δ = 114.0 (br., 1 H), 7.45–7.32 (m, 1 H), 6.55 (d, J = 2.6 Hz, 1 H), 6.43 (d, J = 2.6 Hz, 1 H), 5.48 (dd, J = 17.2, 1.8 Hz, 1 H), 5.29 (d, J = 10.2, 1.8 Hz, 1 H), 3.85 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.1, 165.8, 165.0, 144.7, 138.1, 116.3, 108.8, 102.4, 100.1, 55.4 ppm. IR: $\tilde{\nu}$ = 3450, 2931, 2857, 1653 cm^{-1}. HRMS (ESI): calcd. for $C_{10}H_{10}O_4Na$ $[M + Na]^+$ 217.0477; found 217.0472.

Compound 11: Diisopropyl azodicarboxylate (2 mL, 9.9 mmol) was added at –20 °C to a solution of alcohol **17** (2.5 g, 7.26 mmol), PPh_3 (2.2 g, 8.32 mmol), and 1-phenyl-5-mercapto-1*H*-tetrazole (PT–SH, 1.76 g, 9.9 mmol) in THF (40 mL). The reaction mixture was stirred at 0 °C for 30 min, poured into water, and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous $MgSO_4$, and concentrated in vacuo. The residue was chromatographed over silica gel. Elution with ethyl acetate/petroleum ether (1:3) gave sulfide **18** as a colorless oil. A mixture of $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (1.236 g, 1.0 mmol) and H_2O_2 solution (30%, 5.0 mL) was added at 0 °C to a solution of sulfide **18** (3.4 g, 6.9 mmol) in ethanol (60 mL). The reaction mixture was stirred at room temperature for 6 h, poured into $Na_2S_2O_3$ solution (10%), and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with anhydrous sodium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography; elution with ethyl acetate/petroleum ether (1:5) gave sulfone **11** as a colorless gummy oil in 88% yield (two steps). $[\alpha]_D^{25}$ = +1.67 (c = 1.1, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 7.73–7.54 (m, 4 H), 7.51 (s, 5 H), 7.48–7.33 (m, 6 H), 4.16–4.0 (m, 1 H), 3.92–3.6 (m, 2 H), 2.22–1.96 (m, 2 H), 1.15 (d, J = 6.2 Hz, 3 H), 1.10 (s, 9 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 153.5, 135.9, 135.8, 133.9, 133.4, 133.1, 131.5, 130.0, 129.8, 129.7, 127.9, 127.7, 125.1, 67.3, 52.6, 31.1, 27.1, 23.0, 19.3 ppm. IR: $\tilde{\nu}$ = 3432, 2953, 2041, 1654, 1426 cm^{-1}.

(4*S*,5*S*)-{5-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (20): A solution of 2,3-di-*O*-isopropylidene-D-threitol (**19**, 4 g, 24.7 mmol) in THF (20 mL) was added dropwise over 1 h at room temperature to a suspension of NaH (60% dispersion in mineral oil, 1.98 g, 1.25 mol) in THF (80 mL). The reaction mixture was stirred for an additional 1 h and cooled to 0 °C. A solution of TBSCl (3.73 g, 24.7 mmol) in THF (25 mL) was added dropwise to the mixture over 1 h. Stirring was continued for 30 min, and the reaction mixture was poured into crushed ice (60 mL) and extracted with Et_2O. The organic layer was washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (ethyl acetate/petroleum ether 1:9 then 1:1) on silica gel to afford the monosilylated alcohol (5.78 g, 85%) as a colorless oil. $[\alpha]_D^{25}$ = +12.4 (c = 1.0, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 3.99–3.94 (m, 1 H), 3.87–3.81 (m, 2 H), 3.77–3.62 (m, 3 H), 2.57 (br., 1 H, –OH), 1.39 (s, 3 H), 1.37 (s, 3 H), 0.87 (s, 9 H), 0.05 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 109.2, 80.1, 76.5, 63.7, 62.8, 27.1, 27.0, 25.9, 18.3, –5.45 ppm. IR: $\tilde{\nu}$ = 3442, 2860, 1612, 1518 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{28}O_4SiNa$ $[M + Na]^+$ 299.1655; found 299.1651.

(4*R*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (21): DMSO (2.82 mL, 39.8 mmol) was added at –78 °C to a solution of oxalyl chloride (2.2 mL, 3.16 g, 24.9 mmol) in CH_2Cl_2 (100 mL), and the resulting solution was stirred for 15 min. A solution of the monosilylated alcohol **20** (5.5 g, 19.9 mmol) in CH_2Cl_2 (20 mL) was added dropwise at –78 °C over 30 min. After the solution had been stirred for an additional 30 min, Et_3N (8.38 mL, 59.7 mmol) was added and the reaction mixture was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was poured into aqueous citric acid (10%) and extracted with CH_2Cl_2. The organic layer was washed with saturated aqueous $NaHCO_3$ and brine, dried with $MgSO_4$, and concentrated under reduced pressure to give the crude aldehyde **21** (4.9 g) as a pale yellow oil. $[\alpha]_D^{25}$ = +18.26 (c = 0.8, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 9.75 (d, J = 1.8 Hz, 1 H), 4.34–4.29 (m, 1 H), 4.14–4.08 (m, 1 H), 3.79 (d, J = 4.4 Hz, 2 H), 1.46 (s, 3 H), 1.40 (s, 3 H), 0.88 (s, 9 H), 0.07 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.7, 111.5, 82.0, 63.4, 62.9, 26.8, 26.3, 25.8, 18.3, –5.3, –5.4 ppm. IR: $\tilde{\nu}$ = 1710, 1696, 1598 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{26}O_4SiNa$ $[M + Na]^+$ 297.1498; found 297.1492.

(*S*)-1-{(4*S*,5*S*)-5-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-1,3-dioxolan-4-yl}but-3-en-1-ol (22): A dry round-bottomed flask was charged with (*S*)-BINOL (141 mg, 0.49 mmol) and vacuum-flame-dried powdered molecular sieves (4 Å). The flask was sealed with a septum cap and flushed with N_2. Toluene (30 mL) was added by syringe. Titanium(IV) isopropoxide (73 μL, 0.246 mmol) was added to the resulting stirred suspension dropwise by syringe, resulting in an immediate color change to deep red. After the system had been stirred for 2 h at ambient temperature, aldehyde **21** (4.5 g, 16.42 mmol) was added by syringe over 2 min. After stirring for 5 min, the mixture was cooled to –78 °C in a cooling bath. After this cooling, allyltributylstannane (7.64 mL, 8.16 g, 24.64 mmol) was added by syringe down the sides of the reaction vessel over 5 min. The resulting mixture was stirred for 10 min and was then transferred to a freezer at –15 °C and allowed to stand for 72 h. At this point, direct ^1H NMR analysis of the reaction mixture showed complete consumption of aldehyde. The reaction mixture was concentrated in vacuo to a total volume of ≈60 mL, and the orange/red heterogeneous mixture was loaded directly onto a silica gel column slurry-packed with petroleum ether. The column was eluted with ethyl acetate/petroleum ether (1:10 then 1:5) to afford allylic alcohol **22** (78%) as a pale yellow oil. $[\alpha]_D^{25}$ = –20.57 (c = 1.0, MeOH). ^1H NMR (200 MHz, $CDCl_3$): δ = 5.97–5.86 (m, 1 H), 5.18–5.1 (m, 2 H), 4.31–4.3 (m, 1 H), 3.95–3.84 (m, 1 H), 3.80–3.67 (m, 3 H), 2.50–2.47 (m, 1 H), 2.46–2.22 (m, 1 H), 1.39 (s, 3 H), 1.37 (s, 3 H), 0.90 (s, 9 H), 0.08 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 134.8 (*CH*), 117.8 (CH_2), 109.4, 81.1 (*CH*), 77.3 (*CH*), 70.2 (*CH*), 63.9 (CH_2), 39.3 (CH_2), 27.4 (*Me*), 27.0 (*Me*), 18.5, –5.21 (*Me*), –5.26 (*Me*) ppm. IR: $\tilde{\nu}$ = 3419, 2846, 1616, 1598 cm^{-1}. HRMS (ESI): calcd. for $C_{16}H_{32}O_4SiNa$ $[M + Na]^+$ 339.1968; found 339.1973.

(4*S*,5*S*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-5-[(*S*)-1-(4-methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolane (23): Allyl alcohol **22** (2 g, 6.33 mmol) was taken up in dry THF (30 mL). NaH (60%

dispersion in mineral oil, 253 mg, 6.33 mmol) was then added portionwise at 0 °C. The reaction mixture was stirred at 0 °C for 1 h. Tetrabutylammonium iodide (TBAI, catalytic amount) was added, followed by 4-methoxybenzyl bromide. The reaction mixture was stirred for a further 2 h at room temperature. Water was added carefully to quench any excess of NaH. The mixture was extracted with EtOAc, and the organic solution was washed with water and brine. Concentration and purification by silica gel chromatography (ethyl acetate/petroleum ether 1:10) afforded the PMB-protected compound **23** in 88% yield. $[\alpha]_D^{25}$ = +8.95 (*c* = 1.6, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.9–5.84 (m, 1 H), 5.18–5.06 (m, 2 H), 4.58 (d, *J* = 11.2 Hz, 1 H), 4.5 (d, *J* = 11.2 Hz, 1 H), 4.14–4.0 (m, 2 H), 3.95–3.56 (6 H), 2.41–2.37 (m, 2 H), 1.40 (s, 3 H), 1.39 (s, 3 H), 0.89 (s, 9 H), 0.04 (s, 6 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 159.3, 134.7, 130.6, 129.5, 117.4, 113.8, 109.1, 79.8, 79.1, 76.5, 72.0, 64.3, 55.4, 35.4, 27.4, 27.2, 26.1, 18.5, –5.1, –5.2 ppm. IR: $\tilde{\nu}$ = 2930, 2857, 1612, 1514 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{40}O_5SiNa$ [M + Na]$^+$ 459.2543; found 459.2537.

{(4*S*,5*S*)-5-[(*S*)-1-(4-Methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}methanol (24): The PMB-protected compound **23** (2.4 g, 5.5 mmol) was taken up in dry THF (20 mL). TBAF (1 M in THF, 8.25 mL, 1.5 equiv.) was added, and the reaction mixture was stirred for 2 h at room temperature. After this time, THF was evaporated, water (20 mL) was added, the reaction mixture was extracted with EtOAc (50 mL), and the organic layer was washed with dilute $NaHCO_3$ solution and brine and dried ($MgSO_4$). It was purified by flash chromatography (ethyl acetate/petroleum ether 1:5) to afford compound **24** in 90% yield. $[\alpha]_D^{25}$ = +20.38 (*c* = 1.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.23 (d, *J* = 8.4 Hz, 2 H), 6.86 (d, *J* = 8.4 Hz, 2 H), 5.95–5.84 (m, 1 H), 5.27–5.11 (m, 2 H), 4.62 (d, *J* = 10.8 Hz, 1 H), 4.43 (d, *J* = 10.8 Hz, 1 H), 3.82–3.78 (m, 1 H), 3.73–3.7 (4 H), 3.66–3.53 (m, 3 H), 2.58–2.53 (m, 1 H), 2.52–2.35 (m, 1 H), 1.41 (s, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.3, 133.6 (*CH*), 129.7, (*CH*), 129.6, 117.9 (CH_2), 113.8, (*CH*), 108.9, 80.1 (*CH*), 78.8 (*CH*), 78.4 (*CH*), 71.4 (CH_2), 63.4 (CH_2), 55.1 (*Me*), 35.0 (CH_2), 26.92 (*Me*), 26.91 (*Me*) ppm. IR: $\tilde{\nu}$ = 3461, 2926, 1612, 1513 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{26}O_5Na$ [M + Na]$^+$ 345.1678; found 345.1672.

(4*R*,5*S*)-5-[(*S*)-1-(4-Methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde (10): $NaHCO_3$ (1.58 g, 18.8 mmol) was added to a solution of **24** (1.25 g, 3.76 mmol) in CH_2Cl_2 (25 mL), followed by Dess–Martin periodinane (1 g, 4.14 mmol). After 1 h, a solution (1:1:1) of saturated $NaHCO_3$, saturated $Na_2S_2O_3$, and H_2O (30 mL total) was added. The resulting biphasic mixture was stirred vigorously for 30 min. The layers were separated, and the aqueous fraction was extracted with CH_2Cl_2 (25 mL). The organics were dried, filtered, and concentrated in vacuo. The crude compound was purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:10) to afford aldehyde **10** in 94% yield. $[\alpha]_D^{25}$ = –5.05 (*c* = 1.4, MeOH). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 9.75 (1 H), 7.31 (d, *J* = 8.4 Hz, 2 H), 6.88 (d, *J* = 8.4 Hz, 2 H), 5.96–5.82 (m, 1 H), 5.23–5.12 (m, 2 H), 4.69–4.57 (m, 2 H), 4.42–4.15 (m, 2 H), 3.84 (s, 3 H), 3.83–3.67 (m, 1 H), 2.47–2.38 (m, 2 H), 1.53 (s, 3 H), 1.41 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 200.8 (*CH*), 159.5, 133.8 (*CH*), 130.3, 129.7 (*CH*), 118.2 (CH_2), 113.9 (*CH*), 111.4, 82.4 (*CH*), 78.4 (*CH*), 78.2 (*CH*), 72.4 (CH_2), 55.4 (*Me*), 35.6 (CH_2), 26.8 (*Me*), 25.9 (*Me*) ppm. IR: $\tilde{\nu}$ = 2980, 2931, 1733, 1611 cm^{-1}. HRMS (ESI): calcd. for $C_{18}H_{24}O_5Na$ [M + Na]$^+$ 343.1521; found 343.1516.

(4*S*,5*S*)-4-[(*R*,*E*)-4-*tert*-Butyldiphenylsilyloxypent-1-enyl]-5-[(*S*)-1-(4-methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolane (25): A solution of KHMDS (0.5 M in toluene, 4.32 mL, 2.16 mmol) was added at –98 °C to a solution of sulfone **11** (936 mg, 1.8 mmol) and 18-crown-6 (714 mg, 2.7 mmol) in THF (40 mL). This solution was stirred at –98 °C for 30 min and a solution of aldehyde **10** (600 mg, 1.8 mmol) in THF (10 mL) was added. The reaction mixture was allowed to warm to room temperature over 2 h and poured into saturated NH_4Cl solution. This mixture was extracted with ethyl acetate and the organic layer was washed with saturated $NaHCO_3$ solution and brine. After drying with anhydrous magnesium sulfate, solvent was removed in vacuo and the residue was purified by silica gel column chromatography with ethyl acetate/petroleum ether (1:20) to give **25** (842 mg, 75%) as a colorless oil. $[\alpha]_D^{25}$ = –12.91 (*c* = 1.2, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67–7.43 (m, 4 H), 7.41–7.34 (m, 6 H), 7.22 (d, *J* = 7.6 Hz, 2 H), 6.84 (d, *J* = 7.6 Hz, 2 H), 5.82–5.71 (m, 2 H), 5.43–5.38 (m, 1 H), 5.08–5.03 (m, 2 H), 4.62–4.51 (m, 2 H), 4.39 (t, *J* = 7.6 Hz, 1 H), 3.88–3.84 (m, 1 H), 3.79–3.71 (4 H), 3.64–3.61 (m, 1 H), 2.36–2.05 (m, 4 H), 1.42 (s, 3 H), 1.39 (s, 3 H), 1.05 (12 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.0, 135.7, 134.6, 134.5, 131.6, 131.5, 130.46, 130.4, 129.5, 129.4, 129.2, 127.5, 127.4, 117.2, 113.6, 113.5, 108.5, 82.0, 78.5, 77.8, 72.5, 69.0, 55.2, 42.3, 35.7, 27.0, 26.9, 22.7, 19.1 ppm. IR: $\tilde{\nu}$ = 2960, 2930, 1612, 1513 cm^{-1}. HRMS (ESI): calcd. for $C_{38}H_{50}O_5SiNa$ [M + Na]$^+$ 637.3325; found 637.3319.

(*R*,*E*)-5-{(4*S*,5*S*)-5-[(*S*)-1-(4-Methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pent-4-en-2-ol (9): Compound **25** (770 mg, 1.25 mmol) was taken up in dry THF (10 mL). TBAF (1 M in THF, 2.5 mL, 2 equiv.) was added, and the reaction mixture was stirred for 24 h at room temperature. After this time, THF was removed, water (5 mL) was added, the reaction mixture was extracted with EtOAc (50 mL), and the organic layer was washed with dilute $NaHCO_3$ solution and brine and dried ($MgSO_4$). It was purified by flash chromatography with ethyl acetate/petroleum ether (1:10) to afford compound **9** in 88% yield. $[\alpha]_D^{25}$ = –20.68 (*c* = 1.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.24 (d, *J* = 7.6 Hz, 2 H), 6.85 (d, *J* = 7.6 Hz, 2 H), 5.86–5.54 (m, 3 H), 5.12–5.0 (m, 2 H), 4.58–4.41 (m, 3 H), 3.85–3.61 (6 H), 2.35–2.26 (m, 4 H), 1.42 (s, 3 H), 1.41 (s, 3 H), 1.14 (d, *J* = 6.2 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.2, 134.5, 131.6, 131.4, 130.5, 129.7, 117.5, 113.7, 108.7, 81.9, 79.2, 78.2, 72.4, 67.0, 55.3, 42.2, 35.8, 27.0, 22.8, 22.7 ppm. IR: $\tilde{\nu}$ = 3447, 2982, 2932, 1610 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{32}O_5Na$ [M + Na]$^+$ 399.2147; found 399.2142.

(*R*,*E*)-5-{(4*S*,5*S*)-5-[(*S*)-1-(4-Methoxybenzyloxy)but-3-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pent-4-en-2-yl 2-Hydroxy-4-methoxy-6-vinylbenzoate (26): Triphenylphosphane (546 mg, 2.08 mmol) and DIAD (0.41 mL, 2.08 mmol) were added sequentially to a stirred solution of acid **8** (202 mg, 1.04 mmol) and alcohol **9** (390 mg, 1.04 mmol) in dry toluene (10 mL). After 1.5 h, EtOAc (10 mL) and H_2O (5 mL) were added. The layers were separated and the aqueous phase was extracted with EtOAc (2× 15 mL). The combined organic portions were washed with brine (20 mL), dried with Na_2SO_4, and concentrated under reduced pressure, and the residue was purified by silica gel column chromatography (ethyl acetate/petroleum ether 1:20) to give **26** as a colorless syrup (85%). $[\alpha]_D^{25}$ = –14.727 (*c* = 1.1, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.65 (1 H), 7.23–7.15 (m, 3 H), 6.85 (d, *J* = 7.8 Hz, 2 H), 6.38 (1 H), 6.30 (1 H), 5.78–5.5 (m, 3 H), 5.48–5.07 (m, 5 H), 4.5–4.22 (m, 3 H), 3.69–3.44 (8H), 2.39–2.17 (m, 4 H), 1.32 (s, 3 H), 1.29 (s, 3 H), 1.22 (d, *J* = 6.8 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.6, 165.0, 164.0, 159.2, 143.7, 138.7, 134.5, 132.2, 130.5, 129.5, 129.1, 128.3, 117.4, 115.4, 113.7, 108.8, 108.4, 100.2, 81.9, 78.7, 78.3, 72.4, 72.0, 55.4, 55.3, 38.8, 35.7, 27.0, 26.9, 19.6 ppm. IR: $\tilde{\nu}$ = 3447, 2982, 2933, 1718, 1651 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{40}O_8Na$ [M + Na]$^+$ 575.2621; found 575.2615.

(*R*,*E*)-5-{(4*S*,5*S*)-5-[(*S*)-1-Hydroxybut-3-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}pent-4-en-2-yl 2-Hydroxy-4-methoxy-6-vinylbenzoate (27): Compound **26** (430 mg, 0.778 mmol) was taken up in DCM/H_2O (20 mL, 19:1). DDQ (266 mg, 1.17 mmol) was added in one portion. The reaction mixture was stirred at room temperature for 1 h and filtered, and the filtrate was washed with $NaHCO_3$ (5%) solution, water, and brine. The organic layer was dried ($MgSO_4$) and the solvents were evaporated. Purification by silica gel chromatography (ethyl acetate/petroleum ether 1:10) afforded the pure compound **27** in 86% yield. $[\alpha]_D^{25}$ = –15.57 (*c* = 0.6, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.7 (1 H), 7.30–7.22 (m, 1 H), 6.48 (s, 1 H), 6.39 (s, 1 H), 5.89–5.72 (m, 2 H), 5.71–5.55 (m, 1 H), 5.49–5.43 (m, 1 H), 5.25–5.19 (m, 2 H), 5.13–5.03 (m, 2 H), 4.44–4.41 (m, 1 H), 3.90 (4 H), 3.66–3.61 (m, 1 H), 2.52–2.2.40 (m, 2 H), 2.26–2.03 (m, 2 H), 1.40 (s, 3 H), 1.36 (s, 3 H), 1.31 (d, *J* = 6.4 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.7, 165.2, 164.2, 143.9, 138.7 (*CH*), 134.2 (*CH*), 132.2 (*CH*), 130.4, 129.9 (*CH*), 118.4 (CH_2), 115.6 (CH_2), 109.0, 108.6 (*CH*), 100.4 (*CH*), 82.8 (*CH*), 77.9 (*CH*), 72.2 (*CH*), 70.5 (*CH*), 55.6 (*Me*), 38.9 (CH_2), 37.4 (CH_2), 27.17 (*Me*), 27.13 (*Me*), 19.9 (*Me*) ppm. IR: $\tilde{\nu}$ = 3438, 2922, 2852, 2364, 1634 cm^{-1}. HRMS (ESI): calcd. for $C_{24}H_{32}O_7Na$ $[M + Na]^+$ 455.2046; found 455.2040.

Cochliomycin A: The ester **28** (180 mg, 0.416 mmol) was taken up in anhydrous degassed DCM (200 mL). The second-generation Grubbs metathesis catalyst (25 mg, 0.029 mmol, 7 mol-%) was added and the reaction mixture was allowed to stir at 40 °C for 6 h. The solution was concentrated and the contents of the flask were directly loaded on a silica gel column. Flash chromatography with ethyl acetate/petroleum ether (1:5) afforded pure cochliomycin A in 72% yield as white solid (m.p. 68 °C). $[\alpha]_D^{30}$ = +10.6 (*c* = 0.5, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.5 (s, 1 H), 7.16 (dd, *J* = 15.2, 2.4 Hz, 1 H), 6.47 (d, *J* = 2.4 Hz, 1 H), 6.39 (d, *J* = 2.4 Hz, 1 H), 5.98 (ddd, *J* = 15.0, 8.4, 4.8 Hz, 1 H), 5.72 (ddd, *J* = 15.2, 10.2, 2.8 Hz, 1 H), 5.55–5.48 (m, 1 H), 5.47–5.43 (m, 1 H), 4.56 (t, *J* = 8.0 Hz, 1 H), 4.23–4.19 (m, 1 H), 3.91–3.88 (m, 1 H), 3.81 (s, 3 H), 2.78–2.74 (br., 1 H), 2.55–2.24 (m, 4 H), 1.45 (s, 3 H), 1.44 (d, *J* = 6.4 Hz, 3 H), 1.37 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 170.9, 164.9, 164.0, 142.2, 134.1 (*CH*), 132.8 (*CH*), 129.7 (*CH*), 126.6 (*CH*), 108.5, 107.2 (*CH*), 104.5, 100.2 (*CH*), 81.6 (*CH*), 75.4 (*CH*), 70.6 (*CH*), 69.0 (*CH*), 55.5 (*Me*), 38.0 (CH_2), 36.9 (CH_2), 27.20 (*Me*), 27.18 (*Me*), 19.4 (*Me*) ppm. IR: $\tilde{\nu}$ = 3401, 2929, 2365, 2341, 1680 cm^{-1}. HRMS (ESI): calcd. for $C_{22}H_{28}O_7Na$ $[M + Na]^+$ 427.1733; found 427.1727.

Zeaenol: HCl (2 N, 10 mL) was added to a solution of cochliomycin A (80 mg, 0.198 mmol) in THF (10 mL) and the mixture was stirred for 20 h, quenched with saturated aqueous $NaHCO_3$ solution, and extracted with EtOAc. The organic layers were combined and dried with anhydrous $MgSO_4$, filtered, and concentrated under reduced vacuum. The crude product was purified by flash column chromatography with ethyl acetate/petroleum ether (3:2) to yield zeaenol as a white powder (66 mg, 92%). $[\alpha]_D^{30}$ = –82.0 (*c* = 0.9, MeOH). ^{1}H NMR (400 MHz, $CDCl_3$/CD_3OD = 9:1): δ = 11.92 (s, 1 H), 7.06 (d, *J* = 15.2 Hz, 1 H), 6.4 (s, 1 H), 6.32 (s, 1 H), 5.96–5.82 (m, 2 H), 5.63–5.58 (m, 1 H), 5.30–5.27 (m, 1 H), 4.14–4.05 (m, 1 H), 3.80–3.76 (4 H), 3.52–3.5 (m, 1 H), 2.66–2.56 (br., 3 H, –OH), 2.52–2.14 (m, 4 H), 1.41 (d, *J* = 6.0 Hz, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1, 164.9, 163.9, 142.9, 133.3 (*CH*), 131.1 (*CH*), 129.1 (*CH*), 128.6 (*CH*), 107.5 (*CH*), 103.7, 99.9 (*CH*), 77.3 (*CH*), 77.1 (*CH*), 73.2 (*CH*), 71.3 (*CH*), 55.3 (*Me*), 37.4 (CH_2), 35.7 (CH_2), 19.3 (*Me*) ppm. IR: $\tilde{\nu}$ = 3442, 2932, 2852, 1696, 1598 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$ 387.1420; found 387.1422.

Supporting Information (see footnote on the first page of this article): ^{1}H NMR and ^{13}C NMR spectra for all new compounds and HPLC chromatograms of cochliomycin A and zeaenol.

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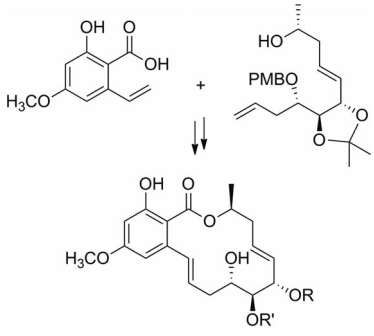
Asymmetric Synthesis

Two resorcylic acid lactones (RALs) – cochliomycin A and zeaenol – have been synthesized for the first time by an enantiodivergent route from the common chiral pool compound L-tartaric acid.



R = R' = $C(Me)_2$; Cochilomycin A
R = H = R'; Zeaenol

Keywords: Lactones / Asymmetric synthesis / Metathesis / Synthetic methods / Macrocycles

