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Asymmetric total synthesis of 5′-*epi*-cochliomycin C

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ABSTRACT

Asymmetric total synthesis of one of the stereoisomers of naturally occurring chlorine containing 14-membered ring macrolide cochliomycin-F (5′-*epi*) has been described in this article. The main highlight of the presented synthetic strategy involves a highly regioselective chlorination and Julia–Kocienski olefination with a highly substituted aromatic chloro-aldehyde to create the required *E*-olefinic unsaturation in the target molecule. Mitsunobu macrolactonization reaction at the late stage enables us to synthesize the target molecule.

1. Introduction

β-Resorcylic acid lactones (RALs) belong to a unique class of fungal polyketide derived secondary metabolite, which are β-resorcylic acid derivatives containing a C11 side chain.[1] In majority of the cases these RALs having a 14-membered ring lactone as one of its core structural component. Their biological activity spans from estrogenic, antifungal, cytotoxic, antimalarial and also have shown to possess inhibitory effect against selective enzymes such as ATPases and kinases.[2] Recently three new 14-membered RALs, two with an unusual natural acetonide group and one with a 5-chloro-substituted lactone, named cochliomycins A–C (**1**–**3**), together with four known analogues, zeaenol (**4**), LL-Z1640-1 (**5**), LL-Z1640-2 (**6**), and paecilomycin F (**7**), were isolated from the culture broth of *Cochliobolus lunatus*, a fungus obtained from the gorgonian *Dichotella gemmacea* collected in the South China Sea (Fig. 1).[1c,3] Recently, RAL based fungal metabolites such as hypothemycin, LL-Z1640-2 and L-783277 have been recognized new class of protein kinase inhibitors.[1e,4] A new family of closely related resocyclic macrolides isolated from the fermentation of *Pochonia chlamydosporia* was recently reported and named pochonins A–F (**8**–**13**), among them five are substituted with a chlorine atom at the aromatic ring (A–E).[1j] Whereas radicicol (**14**) is one of the well-known chlorine containing RAL, found to be the most potent inhibitor of HSV (herpes simplex virus). There exist few synthetic reports for the chloro containing RALs mainly pochonins A–E and radicicol in the literature.[5] We have recently accomplished the total synthesis of cochliomycin-A, zeaenol, and 5′-*epi*-paecilomycin-F for the first time.[6]

At first our goal was to synthesize two natural RALs (peacilomycin F and cochliomycin C) through a common chiral intermediate by a divergent approach. As both of the compounds have a common structural motif with same stereochemical features (except the substitution pattern at the aromatic ring). Asymmetric dihydroxylation by Sharpless protocol was initially thought to create the required two hydroxyl stereocenters at $C_{5'}$ and $C_{6'}$ on a *Z*-substituted α,β-unsaturated ester. During our synthetic efforts toward 5′-*epi*-paecilomycin-F we have observed that, the selectivity of asymmetric dihydroxylation on *Z*-substituted α,β-unsaturated ester by AD-mix β was not up to the mark, whereas the selectivity with the corresponding *E*-olefin was so high, we have decided to carry out the synthesis with the stereochemically pure diol obtained from *E*-olefin, which eventually lead us to 5′-*epi* analogue of the natural product. In the true sense the synthesis presented here is not a target oriented synthesis rather it could be better described as a strategy oriented synthesis as two hydroxyl stereocenters at $C_{5'}$ and $C_{6'}$ have been fixed by asymmetric dihydroxylation by AD-mix β, which lead us to 5′-*epi*-stereocentre. While our efforts toward the total synthesis of several RALs are underway, herein we report the asymmetric total synthesis of 5′-*epi*-cochliomycin-C (**15**). A detailed structure–activity relationship (SAR) with in the RAL family indicates that presence of hydroxyl group at $C_{5'}$ and $C_{6'}$ is essential for increased activity and solubility.[7] As there is no reported relationship between the absolute configuration of those two stereocenters with its biological activity, it might be interesting to synthesize all the possible stereoisomers (variations at $C_{5'}$ and $C_{6'}$) and evaluate their biological profile in detail.

Retrosynthetic analysis of compound **15** is shown in Scheme 1. We envisioned that the double bond between C-1′ and C-2′ can be constructed from the ester **16** by adopting ring closing metathesis (RCM) reaction. Whereas the ester **16** can be accessed from alcohol **17** and highly functionalized aromatic acid **18** containing a pendant vinyl group and required chlorine group by

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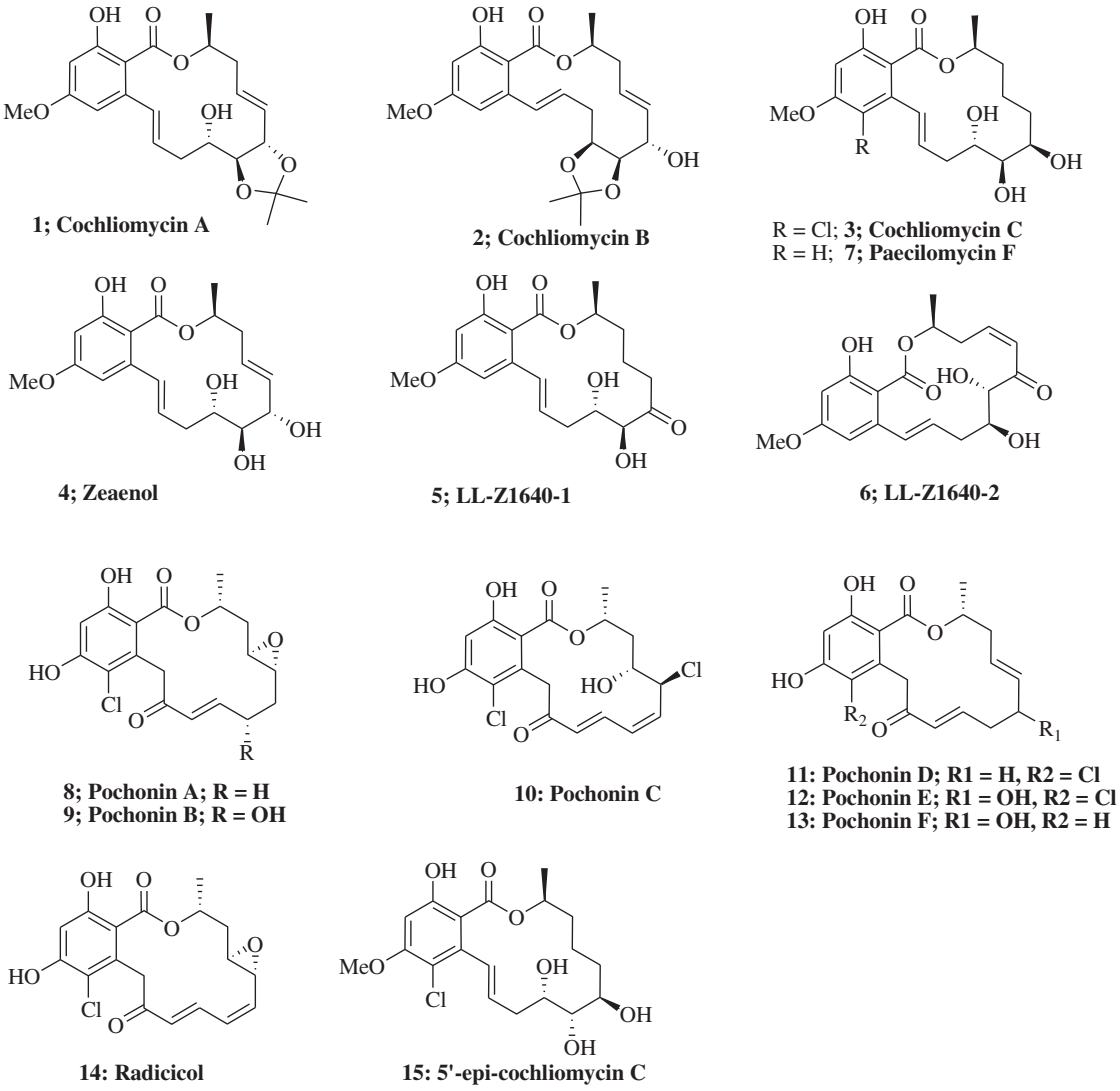
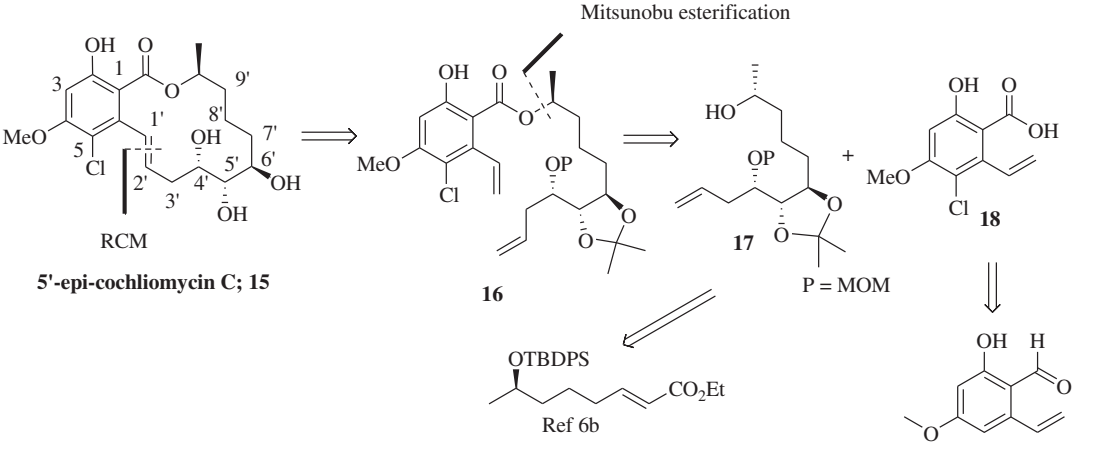


Fig. 1. Structures of cochliomycins, pochonins and other related RALs.



Scheme 1. Retrosynthetic analysis of 5′-*epi*-cochliomycin C.

a Mitsunobu esterification reaction. The alcohol fragment **17** was earlier synthesized in our group[6b] for the total synthesis of 5′-*epi*-paecilomycin-F from 1,5-pentane diol by applying stereoselective Keck allylation, Sharpless asymmetric dihydroxylation, and ME-DKR reaction (metal–enzyme combined dynamic kinetic resolution). The aromatic acid **18** is synthesized by a one-pot oxidation/chlorination sequence starting from the known aldehyde **19**.[6a]

2. Present work

2.1. Synthesis of aromatic acid 18

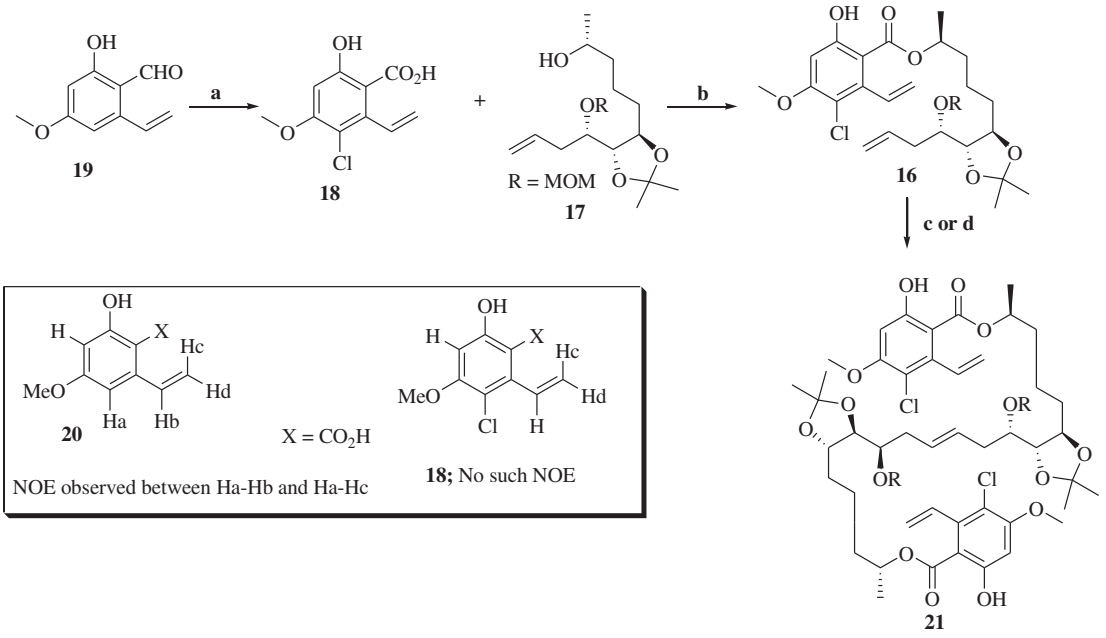
We have started our synthetic venture starting from the known tetrasubstituted aldehyde **19**, which on oxidation under Pinnick condition (with $H_2N{-}SO_3H$ used as a hypochlorous acid scavenger) afforded the acid **18** with the incorporation of the required chlorine group at 3-position (Scheme 2) in 90% yield. The selective incorporation of the Cl atom in the 3-position of compound **18** was proved by NOESY analysis. The acid **20**, which is earlier synthesized in our group[6b] in its $^1H{-}^1H$ NOESY spectrum clearly shows presence of cross-peaks between Ha–Hb and Ha–Hc (Scheme 2; see Supplementary data for the spectrum). Whereas no such cross-peak was observed in the $^1H{-}^1H$ NOESY spectrum of compound **18**. This is a very clear indication that incorporation of the 'Cl' atom took place in the required position.

2.2. Fragment coupling and unsuccessful RCM attempt

Acid **18** is then coupled with the known alcohol **17**[6b] under Mitsunobu condition to afford the ester **16** in 80% yield. Ring closing metathesis reaction is then attempted on ester **16** under various conditions.[9] But to our dismay the required ring-closing product was not obtained, instead cross metathesis (CM) product **21** was obtained in moderate yield (40 and 32%, respectively; Scheme 2). As the crucial RCM reaction failed to yield the desired product, we thought to revise the strategy. The revised strategy was outlined in Scheme 3, where macrolactonization by Mitsunobu inversion reaction was thought to construct the macrocycle. The olefinic unsaturation (between C-1′ and C-2′) with *E*-geometry was planned to construct by Julia–Kocienski olefination (Scheme 3) between aldehyde **23** and sulfone **24**. The sulfone **24** was prepared from the known compound **25**[6b] in just three steps as described below. Whereas aldehyde **23** can be easily accessed from known acid **18**.

2.3. Revised synthetic strategy

Thus when hydroxy-acid **18** was subjected to treatment with acetone in presence of $(CF_3CO)_2O$ it affords the corresponding cyclic ester **26** in 88% yield.[10] The structure of compound **26** was further confirmed by single crystal X-ray analysis (Fig. 2), which proves that incorporation of 'Cl' atom took place in a regioselective manner.



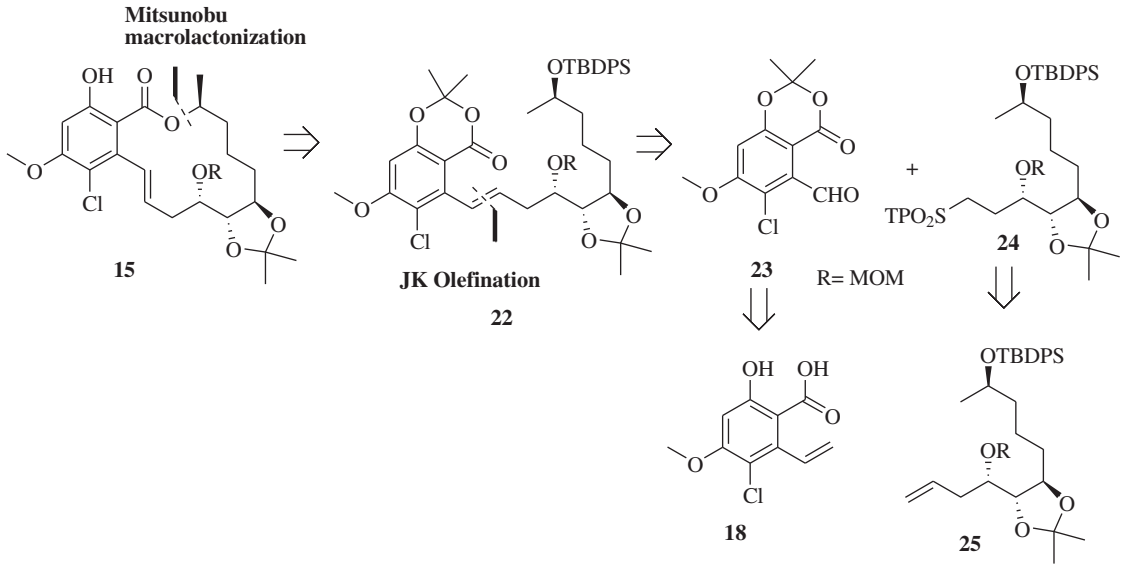
Scheme 2. Reagents and conditions: (a) $NaClO_2$, NH_2SO_3H, THF/H_2O (1:2), 0 °C to rt, 2 h, 90%; (b) DIAD, PPh_3, toluene, 1.5 h, 80%; (c) Grubbs-II (7 mol %), DCM, reflux, 40%; (d) Hoveyda–Grubbs-II, DCM, reflux, 32%.

This one-pot oxidation/electrophilic chlorination reaction is unique as it is very high yielding, affords only one regioisomeric product and depending on the reaction condition incorporation of chlorine may or may not take place in the aromatic nucleus. It is worth mentioning that in our earlier report for the total synthesis of 5′-*epi*-paecilomycin F,[6b] we have synthesized a similar acid without the chlorine atom at 3-position by conducting a Pinnick oxidation of aldehyde **19**, where 2-methyl-2-butene was used as HOCl scavenger. In general for the total synthesis of chlorine containing RALs, researchers used $Ca(OCl)_2$ or SO_2Cl_2 at a late stage as a source of Cl^+ for the incorporation of chlorine group in the aromatic nucleus. Chlorination with SO_2Cl_2 suffers with low regioselectivity whereas with $Ca(OCl)_2$ yields are usually not good.[8]

Oxidative cleavage of **26** afforded aldehyde **23** in a single-pot operation in 82% yield.[11] Whereas compound **25** upon similar oxidative cleavage followed by reduction of the aldehyde functionality afforded alcohol **27**. Compound **27** was then transformed to sulfone **24** by Mitsunobu reaction and oxidation of the sulfide in 84% yield over two steps (Scheme 4).

2.4. Fragment coupling and completion of the synthesis

Next Julia–Kocienski olefination of the sulfone **24** with chloroaldehyde **23** has been attempted.[12] The reaction employing KHMDS as a base and 18-*c*-6 as an additive afforded the desired olefin **22** in 72% yield (*E*/*Z*=12:1). Compound **22** upon treatment with TBAF afforded the alcohol **28** in 88% yield. Removal of the cyclic ester functionality was achieved by treating compound **28** with LiOH in THF/water (2:1) solvent system to furnish hydroxy-acid **29** in 80% yield. Macrolatonization of acid **29** under Mitsunobu inversion condition afforded the desired ring closing lactone **30** in 75% yield.[13] Finally deprotection of acetonide and MOM functionality with 2 N HCl[14] afforded the chloro-RAL 5′-*epi*-cochliomycin C in 90% yield (Scheme 5; overall yield=2.6% from 1,5-pentane diol).



Scheme 3. Revised retrosynthetic strategy involving macrolactonization protocol.

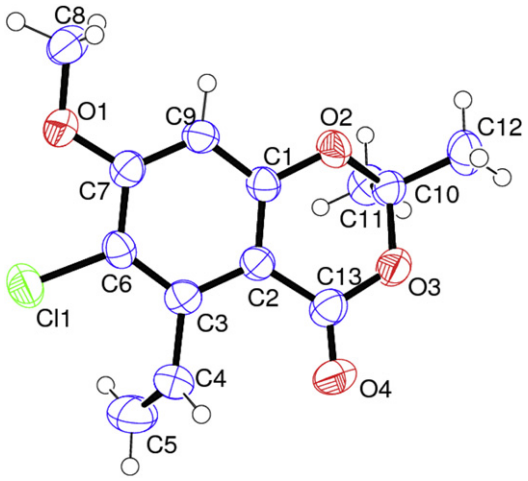


Fig. 2. ORTEP presentation (drawn at 50% probability) of compound **26**.

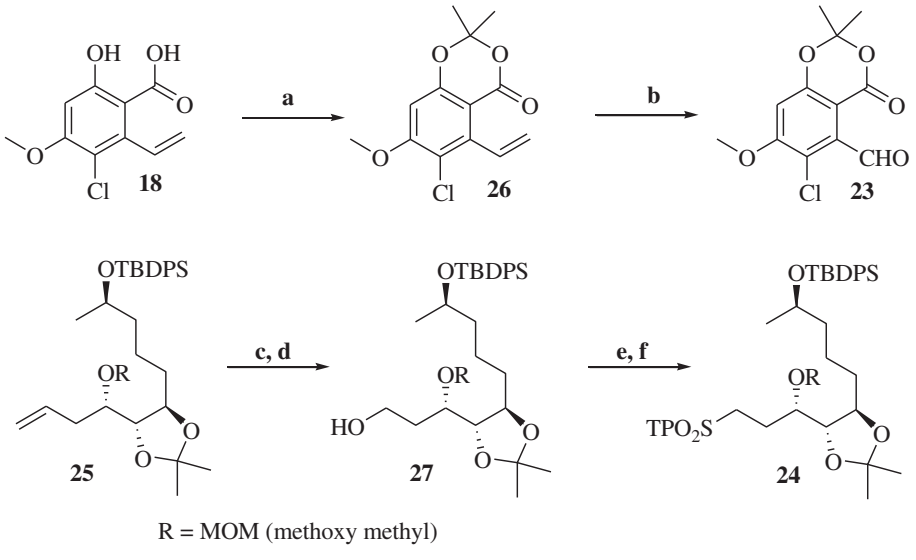
3. Conclusion

In conclusion, we have synthesized new chlorine containing RAL 5′-*epi*-cochliomycin-C in asymmetric fashion. Highlights of our synthetic strategy involved a highly regioselective electrophilic chlorination for the synthesis of penta substituted benzaldehyde, which is then used for Julia–Kocienski olefination. Finally macrolatonization through Mitsunobu esterification method lead to our target molecule. Synthetic studies toward several structurally related RALs (cochliomycins B and C, paecilomycin F) are still under investigation in our laboratory.

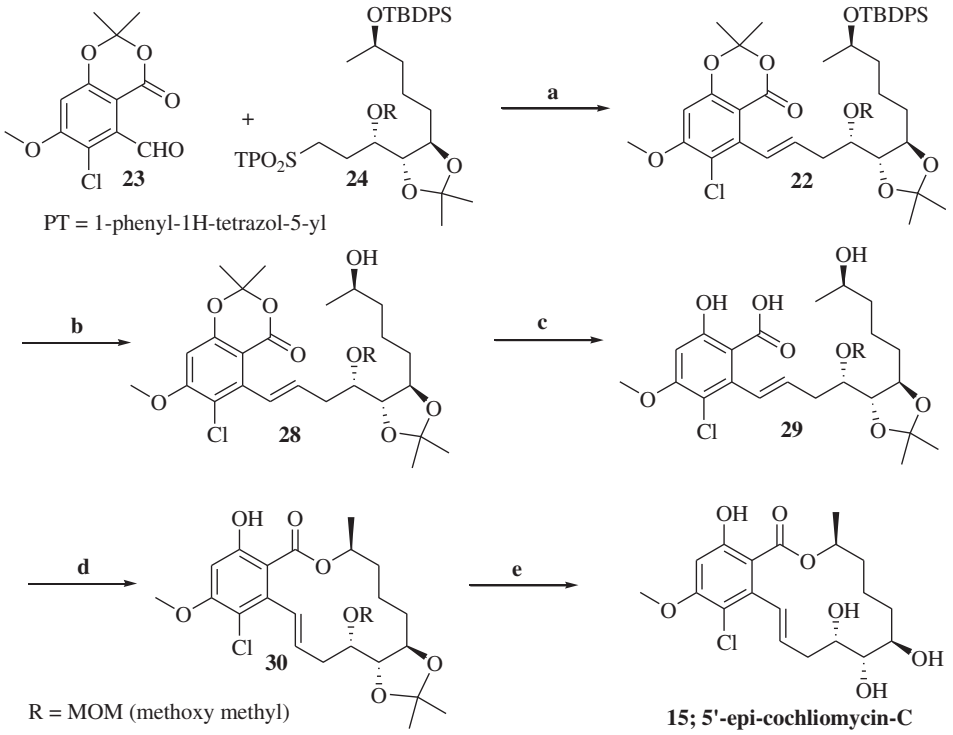
4. Experimental

4.1. General

All moisture and oxygen sensitive reactions were carried out in flame-dried glassware under a nitrogen atmosphere unless otherwise stated. Unless otherwise stated, materials were obtained from commercial suppliers and used without further purification.



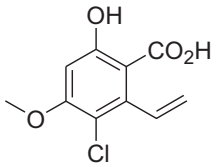
Scheme 4. Reagents and Conditions: (a) $(CF_3CO)_2O$, CH_3COCH_3, H_2SO_4 (cat.), −8 °C, 12 h, 88%; (b) OsO_4, $NaIO_4$, THF/H_2O (3:1), rt, 2 h, 82%; (c) same as b, 88%; (d) $NaBH_4$, MeOH, rt, 1 h, 96%; (e) PTSH, PPh_3, DIAD, THF; (f) $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$, H_2O_2, EtOH (84% in two steps).



Scheme 5. Reagents and conditions: (a) KHMDS, 18-*c*-6, THF, −78 °C, 0.5 h, 72%; (b) TBAF, THF, rt, 4 h, 88%; (c) LiOH·H_2O, THF/H_2O (2:1), 24 h, 80%; (d) DIAD, PPh_3, toluene, 1.5 h, 75%; (e) 2 N HCl, THF, 20 h, 90%.

Tetrahydrofuran and diethylether were distilled from sodiumbenzophenone ketyl. Dichloromethane (DCM), dimethylformamide (DMF), and dimethylsulfoxide (DMSO) were distilled from calcium hydride prior to use. 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. Silica gel 100–200 mesh was used for column chromatography. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated. NMR spectra were recorded on Bruker 400 and 200 MHz spectrometers at 25 °C in $CDCl_3$ using TMS as the internal standard. Chemical shifts are shown in δ. ^{13}C NMR spectra were recorded with a complete proton-decoupling environment. The chemical shift value is listed as δ_H and δ_C for ^1H and ^{13}C, respectively. Melting points are uncorrected. Optical rotations were measured on a JASCO P-1020 digital polarimeter. Mass spectroscopic analysis was performed in the IICT, Hyderabad (TOF analyzer). X-ray data were obtained at IIT-Kharagpur X-ray Crystallography Facility, Department of Chemistry. One of the crystal structure reported in the manuscript (compound **26**) has been deposited to Cambridge Crystallographic Data Centre and the number obtained is CCDC 902974.

4.2. 3-Chloro-6-hydroxy-4-methoxy-2-vinylbenzoic acid (18)



Solution of aldehyde **19** (500 mg, 2.8 mmol) in THF (12 mL) was sequentially treated at 0 °C with sulfamic acid (545 mg, 5.6 mmol) and a solution of sodium chlorite (509 mg, 5.6 mmol) in H_2O (6 mL). After 2 h stirring at room temperature, the reaction mixture was diluted with EtOAc. The layers were separated, and it was washed with saturated NH_4Cl solution. The organic solvent was dried ($MgSO_4$), filtered, and concentrated in vacuum to afford the crude acid. The crude material was then purified by flash column chromatography with EtOAc/petroleum ether (1:3) to yield the corresponding acid **18** (575 mg) as brown solid in 90% yield. Mp 128–130 °C.

R_f=0.3 (EtOAc/hexane; 2:1).

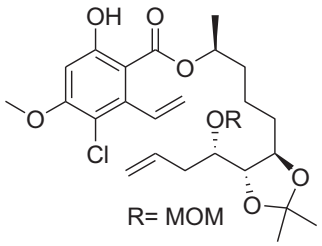
IR (ν): 3400, 2982, 2933, 1710 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 11.3 (br, 1H), 6.87 (dd, J=17.6, 11.6 Hz, 1H), 6.51 (s, 1H), 5.61 (d, J=11.6 Hz, 1H), 5.31 (d, J=17.6 Hz, 1H), 3.94 (s, 3H).

δ_C ($CDCl_3$, 50 MHz): 173.9, 163.5, 160.5, 141.4, 134.0, 120.5, 114.1, 104.2, 99.6, 56.4.

HRMS (ESI) for $C_{10}H_9ClO_4Na$ $[M+Na]^+$, calculated: 251.0087, found: 251.0083.

4.3. (*S*)-5-((4*R*,5*R*)-5-((*S*)-1-(Methoxymethoxy)but-3-enyl)-2,2-dimethyl-1,3-dioxolan-4-yl)pentan-2-yl 2-hydroxy-4-methoxy-5-chloro-6-vinylbenzoate (16)



Triphenylphosphine (Ph_3P, 210 mg, 0.8 mmol) and DIAD (0.16 mL, 0.8 mmol) were added sequentially to a stirred solution of acid **18** (92 mg, 0.4 mmol) and alcohol **17** (113 mg, 0.4 mmol) in dry toluene (4 mL). After completion of the reaction as indicated by TLC analysis, EtOAc (10 mL) and H_2O (5 mL) were added to the reaction solution. The layers were separated and the aqueous phase was extracted with EtOAc (2×15 mL). The combined organic portions were washed with brine, dried with $MgSO_4$, and concentrated under reduced pressure to afford the crude residue, which was then purified by

silica gel column chromatography with EtOAc/petroleum ether (1:20) to afford ester **16** (165 mg) as a colorless syrup (85%).

R_f=0.4 (EtOAc/hexane, 1:10).

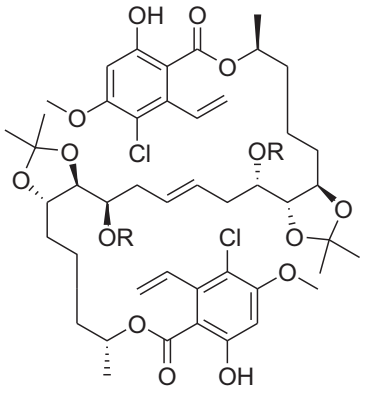
IR (ν): 3440, 2982, 2933, 1705, 1651 cm^{-1}.

$[\alpha]_D^{25}$ −21.7 (*c* 0.4, MeOH). δ_H ($CDCl_3$, 400 MHz): 11.48 (s, 1H), 6.81 (dd, *J*=17.6, 11.6 Hz, 1H), 6.5 (s, 1H), 5.87–5.81 (m, 1H), 5.46 (d, *J*=11.6 Hz, 1H), 5.26–5.06 (m, 4H), 4.68 (s, 2H), 3.9 (s, 3H), 3.88–3.86 (m, 1H), 3.71–3.65 (m, 2H), 3.38 (s, 3H), 2.42–2.29 (m, 2H), 1.60–1.32 (m, 6H), 1.42 (s, 3H), 1.40 (s, 3H), 1.22 (d, *J*=6.0 Hz, 3H).

δ_C ($CDCl_3$, 100 MHz): 170.5, 162.6, 159.7, 141.1, 134.8, 134.6, 119.1, 117.8, 113.8, 108.6, 106.1, 99.6, 96.5, 81.9, 77.8, 76.0, 73.3, 56.5, 56.0, 35.9, 33.5, 27.5, 27.1, 22.3, 19.9.

HRMS (ESI) for $C_{26}H_{37}ClO_8Na$ $[M+Na]^+$, calculated: 535.2075, found: 535.2078.

4.4. Dimer 21



The ester **16** (152 mg, 0.3 mmol) was taken in anhydrous degassed DCM (150 mL). The second-generation Grubbs metathesis catalyst (18 mg, 7 mol %) was then added and the reaction mixture was allowed to stir at 40 °C for 8 h. The solution was concentrated and the contents of the flask were directly loaded on a silica gel column. Flash chromatography with EtOAc/petroleum ether (1:3) afforded the dimer **21** (119 mg, 40%).

The ester **16** was treated with Hoveyda–Grubbs-II (5 mol %) catalyst in the same manner to afford the dimer **21** (96 mg, 32%).

R_f=0.2 (EtOAc/hexane, 1:7).

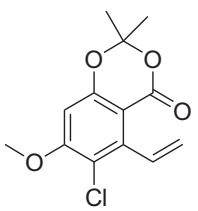
IR (ν): 3400, 3012, 2935, 2372, 2341, 1698 cm^{-1}.

$[\alpha]_D^{25}$ −82.5 (*c* 1.0, MeOH). δ_H ($CDCl_3$, 400 MHz): 11.5 (s, 2H), 6.88 (dd, *J*=17.4, 11.2 Hz, 2H), 6.5 (s, 2H), 5.74–5.68 (m, 2H), 5.48 (d, *J*=11.2 Hz, 2H), 5.3–5.1 (m, 4H), 4.81–4.77 (m, 4H), 3.95 (s, 6H), 3.94–3.90 (m, 2H), 3.7–3.65 (m, 4H), 3.4 (s, 6H), 2.48–2.40 (m, 4H), 1.62–1.48 (m, 12H), 1.4–1.3 (12H), 1.26 (d, *J*=6.0 Hz, 6H).

δ_C ($CDCl_3$, 100 MHz): 170.3, 162.4, 159.6, 140.9, 134.7, 128.7, 118.9, 113.7, 108.6, 106.0, 99.5, 96.2, 81.4, 78.5, 77.5, 73.1, 56.4, 55.8, 35.7, 34.5, 34.3, 27.4, 27.0, 22.2.19.7.

HRMS (ESI) for $C_{52}H_{74}Cl_2O_{16}Na$ $[M+Na]^+$, calculated: 1047.4252, found: 1047.4251.

4.5. 6-Chloro-7-methoxy-2,2-dimethyl-5-vinyl-4*H*-benzo[*d*][1,3]dioxin-4-one (26)



In a 10 mL round-bottomed flask equipped with a magnetic stirring bar was charged with acid **18** (525 mg, 2.3 mmol), trifluoroacetic anhydride (0.4 mL), and anhydrous acetone (2 mL). The mixture was then cooled to −8 °C and catalytic amount of concentrated H_2SO_4 was added to the stirring mixture. The flask was then kept at −8 °C for 12 h with stirring. After that time a saturated solution of aqueous $NaHCO_3$ was poured into the reaction mixture, and extracted with ethyl acetate (3×20 mL). The combined organic extracts were washed with water and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated to give a brown residue. Chromatography of the crude residue over silica using EtOAc/petroleum ether (1:5) gave acetonide **26** (545 mg, 88%) as white solid.

R_f=0.7 (EtOAc/hexane, 1:5). Mp 105–107 °C.

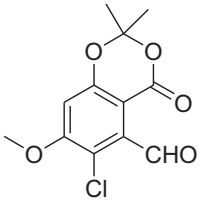
IR (ν): 2930, 2372, 1705 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 7.0 (dd, *J*=17.6, 11.6 Hz, 1H), 6.43 (s, 1H), 5.67 (d, *J*=11.6 Hz, 1H), 3.92 (s, 3H), 1.7 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 160.9, 159.2, 156.9, 141.6, 132.2, 121.6, 116.9, 105.5, 105.3, 99.2, 56.7, 25.6.

HRMS (ESI) for $C_{13}H_{13}ClO_4Na$ $[M+Na]^+$, calculated: 291.0400, found: 291.0405.

4.6. 6-Chloro-7-methoxy-2,2-dimethyl-4-oxo-4*H*-benzo[*d*][1,3]dioxine-5-carbaldehyde (23)



Dihydroxylation of olefinic compound **26** and consecutive oxidative cleavage were performed in single-pot operation. To a stirring solution of the olefin **26** (520 mg, 1.94 mmol) in THF/H_2O (3:1) at room temperature NMO (681.8 mg, 5.82 mmol), 0.05 M solution of OsO_4 in toluene (7.76 mL, 0.38 mmol), and $NaIO_4$ (1.24 g, 5.82 mmol) were added sequentially. The mixture was then stirred vigorously at room temperature for 3 h, and then quenched by the addition of saturated aqueous Na_2SO_3 solution. The solution was extracted then with EtOAc. The combined organic layers were washed with aqueous $NaHCO_3$ solution, dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the crude residue was accomplished by flash column chromatography eluting with EtOAc/petroleum ether (1:7) to afford the aldehyde **23** (430 mg, 82%) as white solid.

R_f=0.45 (EtOAc/hexane, 1:5). Mp 110–113 °C.

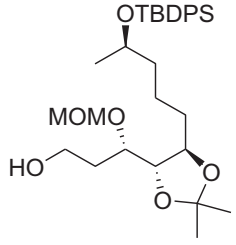
IR (ν): 2825, 1720, 1700 cm^{-1}.

δ_H ($CDCl_3$, 200 MHz): 10.4 (s, 1H), 6.57 (s, 1H), 3.96 (s, 3H), 1.75 (s, 6H).

δ_C ($CDCl_3$, 50 MHz): 190.8, 161.7, 159.3, 156.9, 140.3, 115.3, 107.2, 104.8, 101.7, 57.2, 25.8.

HRMS (ESI) for $C_{12}H_{11}ClO_5Na$ $[M+Na]^+$, calculated: 293.0193, found: 293.0198.

4.7. (*S*)-3-(Methoxymethoxy)-3-((4*R*,5*R*)-5-((*R*)-4-*tert*-butyldiphenylsilyloxy-pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl) propan-1-ol (27)



The olefin **25** was converted to corresponding aldehyde by dihydroxylation and oxidative cleavage with $OsO_4/NaIO_4$ in one-pot reaction as discussed earlier for compound **23**. The aldehyde was then reduced with $NaBH_4$ as follows.

To a stirring solution of the crude aldehyde (1 g, 1.84 mmol) in MeOH (10 mL) at 0 °C $NaBH_4$ (105 mg, 2.76 mmol, 1.5 equiv) was added. Stirring was continued for 1 h at 0 °C after which the reaction was quenched with the slow addition of saturated aqueous NH_4Cl solution and then it was diluted with EtOAc. The layers were then separated and the aqueous layer was extracted with EtOAc (3×15 mL). The organic layer was washed with water, brine and then dried over $MgSO_4$. The organic solvent was concentrated under reduced pressure to provide the crude alcohol **27**. The crude mixture was then purified by flash column chromatography eluting with EtOAc/petroleum ether (1:5) to afford the alcohol **27** (930 mg, 93%).

R_f=0.55 (EtOAc/hexane; 1:5).

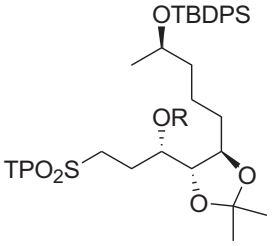
IR (ν): 3380, 2930 cm^{-1}.

$[\alpha]_D^{25}$ +11.5 (*c* 0.6, MeOH). δ_H ($CDCl_3$, 200 MHz): 7.71–7.68 (m, 4H), 7.41–7.32 (m, 6H), 4.77–4.68 (m, 2H), 3.88–3.62 (m, 6H), 3.41 (s, 3H), 3.0 (br, 1H, –OH), 1.81–1.69 (m, 2H), 1.48–1.40 (m, 6H), 1.38 (s, 6H), 1.0 (s, 12H).

δ_C ($CDCl_3$, 50 MHz): 135.9, 134.8, 134.5, 129.5, 129.5, 127.5, 127.4, 108.4, 97.3, 83.1, 77.8, 74.9, 69.4, 58.6, 56.1, 39.3, 34.0, 33.6, 27.4, 27.1, 26.9, 23.1, 21.7, 19.3.

HRMS (ESI) for $C_{31}H_{48}O_6SiNa$ $[M+Na]^+$, calculated: 567.3118, found: 567.3114.

4.8. 5-((*S*)-3-(Methoxymethoxy)-3-((4*R*,5*R*)-5-((*R*)-4-*tert*-butyldiphenylsilyloxy-pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl) propylsulfonyl)-1-phenyl-1*H*-tetrazole (24)



Diisopropyl azodicarboxylate (0.42 mL, 2.1 mmol) was added to a solution of alcohol **27** (880 mg, 1.61 mmol), PPh_3 (472 mg, 1.8 mmol), and 1-phenyl-5-mercapto-1*H*-tetrazole [PT-SH] (375 mg, 2.1 mmol) in THF (10 mL) at –20 °C. The solution was stirred at 0 °C for 30 min, then the reaction mixture was 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 vacuum to afford the crude sulfide. To the solution of the crude sulfide in ethanol (15 mL) were added $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ (299 mg, 0.242 mmol) and 30% H_2O_2 solution (1.2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then it was poured into 10% $Na_2S_2O_3$ solution and extracted with ethyl acetate. The organic layer was washed with saturated $NaHCO_3$ solution and brine, dried with $MgSO_4$, and concentrated in vacuo. The residue was purified over silica gel column chromatography by eluting with EtOAc/petroleum ether (1:7) to afford the sulfone **24** (1.04 g) as colorless gummy oil in 88% yield (two steps).

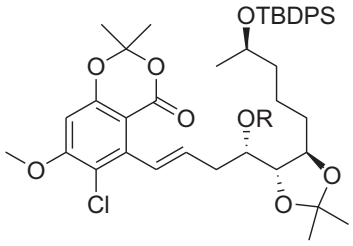
R_f=0.6 (EtOAc/hexane; 1:5).

$[\alpha]_D^{25}$ +12.45 (*c* 0.9, MeOH). δ_H ($CDCl_3$, 400 MHz): 7.73–7.62 (m, 9H), 7.43–7.28 (m, 6H), 4.72–4.68 (m, 2H), 4.07–4.03 (m, 1H), 3.96–3.86 (m, 3H), 3.65–3.61 (m, 2H), 3.40 (s, 3H), 2.39–2.33 (m, 1H), 2.20–2.17 (m, 1H), 1.52–1.5 (m, 6H), 1.4 (s, 6H), 1.08 (12H).

δ_C ($CDCl_3$, 50 MHz): 153.5, 135.9, 134.8, 134.6, 133.1, 131.5, 129.7, 129.5, 129.4, 127.5, 127.4, 125.1, 108.8, 96.8, 82.6, 77.8, 74.1, 69.4, 56.3, 52.8, 39.3, 33.5, 27.5, 27.1, 26.8, 24.7, 23.1, 21.7, 19.3.

HRMS (ESI) for $C_{38}H_{52}N_4O_7SSiNa$ $[M+Na]^+$, calculated: 759.3224, found: 759.3229.

4.9. 6-Chloro-7-methoxy-5-((*S*,*E*)-4-(methoxymethoxy)-4-((4*R*,5*R*)-5-((*R*)-4-*tert*-butyldiphenylsilyloxy-pentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)but-1-enyl)-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (22)



To a solution of sulfone **24** (580 mg, 0.786 mmol) and 18-crown-6-ether (311 mg, 1.18 mmol) in THF (10 mL) was added 0.5 M solution of KHMDS in toluene (1.84 mL, 0.92 mmol) at –78 °C. The mixture was stirred at –78 °C for 30 min, a solution of aldehyde **23** (265 mg, 0.98 mmol) in THF (3 mL) was then added into this solution. The reaction mixture was allowed to warm to room temperature for 2 h and poured into saturated NH_4Cl solution. This mixture was then extracted with ethyl acetate and the organic layer was washed with saturated $NaHCO_3$ solution and brine. After drying with anhydrous $MgSO_4$, solvent was removed in vacuo, and the residue purified by silica gel column chromatography with EtOAc/petroleum ether (1:5) gave olefin **22** (560 mg) in 75% yield.

R_f=0.5 (EtOAc/hexane; 1:5).

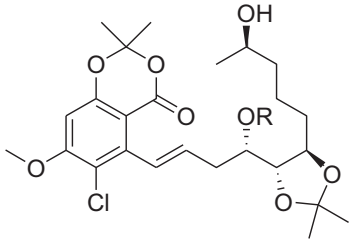
IR (ν): 2935, 1698 cm^{-1}.

$[\alpha]_D^{25}$ +19.0 (*c* 2.0, MeOH). δ_H ($CDCl_3$, 400 MHz): 7.68–7.65 (m, 4H), 7.4–7.34 (m, 6H), 6.76 (d, *J*=18.0 Hz, 1H), 6.43 (s, 1H), 5.97–5.93 (m, 1H), 4.78 (d, *J*=6.8 Hz, 1H), 4.68 (d, *J*=6.8 Hz, 1H), 3.93 (s, 3H), 3.93–3.88 (m, 1H), 3.86–3.74 (m, 3H), 3.37 (s, 3H), 2.68–2.58 (m, 2H), 1.71–1.5 (m, 6H), 1.42 (s, 3H), 1.38 (s, 3H), 1.0 (12H).

δ_C ($CDCl_3$, 100 MHz): 160.7, 159.0, 156.8, 141.1, 135.8, 134.8, 134.4, 133.8, 129.7, 129.4, 129.3, 128.9, 128.1, 127.4, 127.3, 117.0, 108.2, 105.3, 98.8, 96.3, 81.6, 77.3, 75.7, 69.4, 56.5, 55.8, 39.3, 35.2, 33.4, 27.3, 26.9, 25.5, 25.4, 22.9, 21.7, 19.2.

HRMS (ESI) for $C_{43}H_{57}ClO_9SiNa$ $[M+Na]^+$, calculated: 803.3358, found: 803.3362.

4.10. 6-Chloro-5-((*S*,*E*)-4-((4*R*,5*R*)-5-((*R*)-4-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)but-1-enyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (28)



Compound **22** (420 mg, 0.54 mmol) was taken in dry THF (10 mL). TBAF (1 M in THF, 1.1 mL, 0.11 mmol) was added to it, and the reaction mixture was stirred for 24 h at room temperature. After this time, THF was evaporated, and water (2 mL) was added to it. The reaction mixture was then extracted with EtOAc (25 mL). The

organic layer was washed successively with dilute $NaHCO_3$ solution and brine. The organic solvent was dried with $MgSO_4$ and evaporated in vacuo to afford the crude product, which was purified by flash chromatography with EtOAc/petroleum ether (1:3) to afford the compound **28** (258 mg) in 88% yield.

R_f=0.35 (EtOAc/hexane; 1:5).

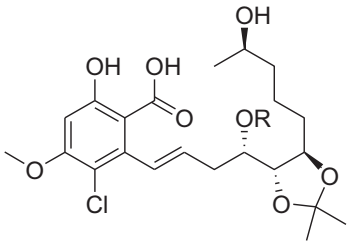
IR (ν): 3330, 2920, 2340, 1710 cm^{-1}.

$[\alpha]_D^{25}$ +9.67 (*c* 0.8, MeOH). δ_H ($CDCl_3$, 400 MHz): 6.79 (d, *J*=16.0 Hz, 1H), 6.44 (s, 1H), 6.0–5.92 (m, 1H), 4.8 (d, *J*=6.8 Hz, 1H), 4.71 (d, *J*=6.8 Hz, 1H), 4.04–4.0 (m, 1H), 3.95 (s, 3H), 3.91–3.88 (m, 1H), 3.85–3.71 (m, 2H), 3.39 (s, 3H), 2.74–2.59 (m, 2H), 1.51–1.48 (m, 6H), 1.44 (s, 3H), 1.41 (s, 3H), 1.2 (d, *J*=6.0 Hz, 3H).

δ_C ($CDCl_3$, 100 MHz): 160.9, 159.3, 157.2, 141.4, 133.9, 127.7, 117.3, 108.5, 105.6, 105.5, 99.1, 96.6, 81.8, 77.5, 76.0, 69.0, 56.8, 56.1, 39.3, 35.4, 33.4, 27.6, 27.2, 25.8, 25.7, 23.6, 22.5.

HRMS (ESI) for $C_{27}H_{39}ClO_9Na$ $[M+Na]^+$, calculated: 565.2180, found: 565.2185.

4.11. 3-Chloro-6-hydroxy-2-((*S*,*E*)-4-((4*R*,5*R*)-5-((*R*)-4-hydroxypentyl)-2,2-dimethyl-1,3-dioxolan-4-yl)-4-(methoxymethoxy)but-1-enyl)-4-methoxybenzoic acid (29)



To a solution of compound **28** (180 mg, 0.33 mmol) in THF (4 mL) was added $LiOH \cdot H_2O$ (54 mg, 1.3 mmol) in H_2O (2 mL) at 0 °C. After completion of the hydrolysis (approximately 20 H), 0.5 N HCl was slowly added till the solution becomes acidic and it was diluted with EtOAc. The layers were then separated and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to give the seco-acid as sticky oil. It was then purified by flash chromatography with EtOAc/petroleum ether (1:1) to afford the pure compound **29** (133 mg) in 80% yield.

R_f=0.25 (EtOAc/hexane; 1:1).

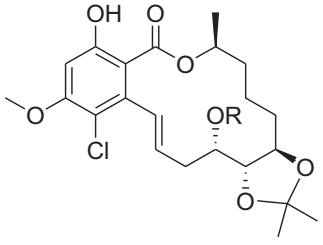
IR (ν): 3400, 2930, 2372, 2341, 1690 cm^{-1}.

$[\alpha]_D^{25}$ +19.67 (*c* 0.4, MeOH). δ_H ($CDCl_3$, 400 MHz): 11.8 (br, 1H), 6.59 (d, *J*=16.0 Hz, 1H), 6.44 (s, 1H), 5.70–5.62 (m, 1H), 4.78 (d, *J*=6.8 Hz, 1H), 4.7 (d, *J*=6.8 Hz, 2H), 4.1–4.04 (m, 1H), 3.94 (s, 3H), 3.92–3.7 (m, 3H), 3.40 (s, 3H), 2.67–2.52 (m, 2H), 1.65–1.53 (m, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 1.18 (d, *J*=6.0 Hz, 3H).

δ_C ($CDCl_3$, 100 MHz): 173.8, 163.4, 160.1, 140.8, 131.1, 130.0, 114.3, 108.6, 105.3, 99.5, 99.2, 81.7, 77.6, 76.3, 68.4, 56.5, 56.1, 38.5, 35.0, 33.4, 27.6, 27.0, 23.6, 21.7.

HRMS (ESI) for $C_{24}H_{35}ClO_9Na$ $[M+Na]^+$, calculated: 525.1867, found: 525.1862.

4.12. Compound 30



To a solution of PPh_3 (209 mg, 0.8 mmol) and DIAD (0.157 mL, 0.8 mmol) in 50 mL of anhydrous toluene under N_2 atmosphere at −10 °C was added a solution of seco-acid **29** (100 mg, 0.2 mmol) in 50 mL toluene via syringe pump over 1 h. The resulting mixture was then slowly allowed to warm at room temperature. After disappearance of starting material as indicated by TLC, the reaction mixture was concentrated and the crude material was purified by flash chromatography on silica gel with EtOAc/petroleum ether (1:10) to afford the macrolactone **30** (73 mg) in 75% yield.

R_f=0.5 (EtOAc/hexane; 1:5).

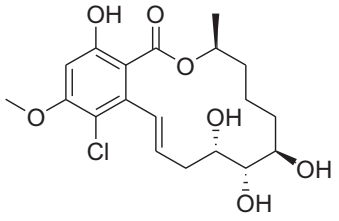
IR (ν): 2929, 2365, 2341, 1680 cm^{-1}.

$[\alpha]_D^{25}$ +22.4 (*c* 0.5, MeOH). δ_H ($CDCl_3$, 400 MHz): 11.8 (br, 1H, Ar–OH), 6.56 (d, *J*=16.0 Hz, 1H), 6.45 (s, 1H), 6.0 (td, *J*=16.0, 6.8 Hz, 1H), 5.25–5.20 (m, 1H), 4.8 (d, *J*=6.8 Hz, 1H), 4.73 (d, *J*=6.8 Hz, 1H), 3.94 (s, 3H), 3.88–3.68 (m, 3H), 3.42 (s, 3H), 2.74–2.50 (m, 2H), 1.78–1.52 (m, 6H), 1.43 (s, 3H), 1.41 (s, 3H), 1.1 (d, *J*=6.2 Hz, 3H).

δ_C ($CDCl_3$, 100 MHz): 171.0, 163.1, 160.0, 142.5, 134.0, 128.6, 113.6, 109.0, 104.7, 99.8, 95.9, 82.0, 77.5, 76.3, 70.6, 56.8, 56.0, 35.3, 34.9, 32.8, 27.7, 27.3, 20.9, 20.6.

HRMS (ESI) for $C_{24}H_{33}ClO_8Na$ $[M+Na]^+$, calculated: 507.1762, found: 507.1766.

4.13. 5′-*epi*-Cochliomycin C



To a solution of compound **30** (50 mg, 0.103 mmol) in THF (5 mL) was added HCl (2 N, 5 mL) and the mixture was then stirred for 20 h at room temperature. The reaction was then quenched with saturated aqueous $NaHCO_3$ solution and extracted with EtOAc. The organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure to afford the crude product, which was the purified by flash column chromatography with EtOAc/petroleum ether (3:2) to afford 5-*epi*-Cochliomycin C as a white powder (37 mg, 90%).

R_f=0.3 (EtOAc/hexane, 2:1).

IR (ν): 3440, 2930, 2852, 1690, 1598 cm^{-1}.

$[\alpha]_D^{25}$ +41.7 (*c* 0.5, MeOH). δ_H ($CDCl_3$, 400 MHz): 12.02 (br, 1H, Ar–OH), 6.57 (d, *J*=16.0 Hz, 1H), 6.47 (s, 1H), 5.95–5.87 (m, 1H), 5.19–5.12 (m, 1H), 3.9 (s, 3H), 3.94–3.9 (m, 1H), 3.7–3.67 (m, 1H), 3.48–3.45 (m, 1H), 2.89–2.85 (m, 1H), 2.52–2.45 (m, 1H), 1.88–1.67 (m, 6H), 1.32 (d, *J*=6.2 Hz, 3H). δ_C ($CDCl_3$, 100 MHz): 171.0, 163.3, 160.3, 140.6, 131.1, 128.8, 114.9, 105.6, 99.8, 73.6, 70.9, 69.8, 67.4, 56.0, 35.8, 34.8, 32.4, 21.5, 21.2. HRMS (ESI) for $C_{19}H_{25}ClO_7Na$ $[M+Na]^+$, calculated: 423.1187, found: 423.1182.

Acknowledgements

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Supplementary data

Copies of the ^{1}H NMR and ^{13}C NMR spectra for all key intermediates and final product. Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.02.033.

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