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Asymmetric total synthesis of filamentous fungi related resorcylic acid lactones 7-*epi*-zeaenol and zeaenol

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Abstract: An efficient, short and, a convenient asymmetric total synthesis of filamentous fungi related resorcylic acid lactones 7-epi-zeaenol (**2**) and zeaenol (**1**) have been achieved in 7 and 9 linear steps with the high overall yield of 32% and 21% respectively, from the known intermediate **13**. Mitsunobu inversion, De Brabander's protocol for macrolactonisation, Heck cross-coupling, diastereoselective alkyne aldehyde coupling and Ohira–Bestmann alkynylation are the key reactions.

Keywords: Macrolactonisation, Natural products, Asymmetric synthesis, Heck cross coupling, C-C bond formation.

Introduction

Filamentous fungi possess an enormously rich source of biologically active natural products and have immense applications in various fields. Modern synthetic chemistry has enabled the identification, isolation, and manufacturing many of the promising biologically active filamentous fungi related natural products [1-3]. Included in this natural product family, highly oxygenated natural products zeaenol and 7-*epi*-zeaenol (Figure 1) are isolated by Oberlies and co-workers [4,5] from a filamentous fungus, MSX 63935, collected from the leaf litter in Nigeria, along with other natural products. These resorcylic acid lactones (RALs) exhibit potent antibacterial activity as well as mitochondrial transmembrane potential activity. Of them, zeaenol (**1**) and 7-*epi*-zeaeneol (**2**) showed cytotoxic activity against human tumor cell lines [6,7] with nearly same IC_{50} values (IC_{50} values >50 μM) and inhibition activity towards NF-κB. The first total synthesis of zeaenol along with its analog cochliomycin A was reported by Nanda *et al* [8] using late stage ring closing metathesis (RCM) strategy. Later, several synthetic procedures [9-13] for the total synthesis of zeaenol and 7-*epi*-zeaenol have been developed using diverse methods. In continuation of our efforts on the total synthesis of biologically active lactonic natural products [14-21], herein we described a first asymmetric total synthesis of zeaenol and 7-*epi*-zeaenol.

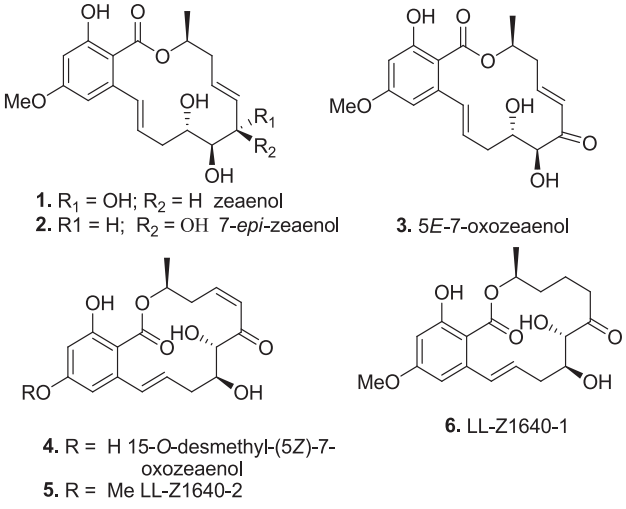

Figure 1. Structures of filamentous fungi derived resorcylic acid lactones (1-6).

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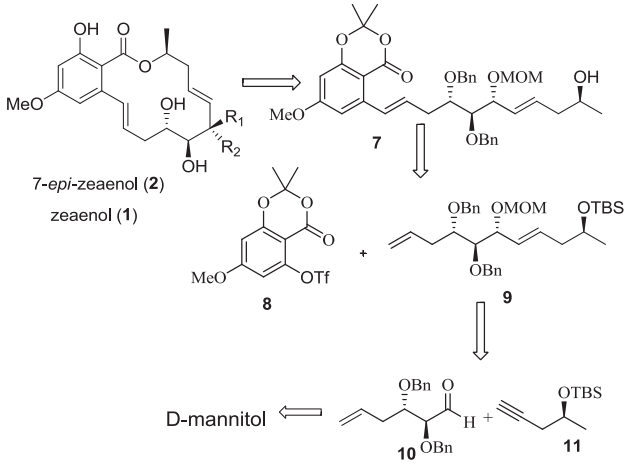
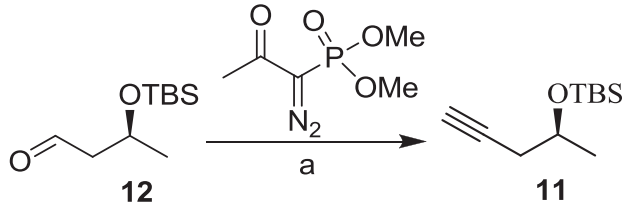
Result and discussion

The retrosynthetic analysis of zeaenol and 7-*epi*-zeaenol is depicted in Scheme 1. The target molecules **1** and **2** could be derived from the common fragment **7** following De Brabander's lactonization, which could be obtained by the aromatic fragment **8** and aliphatic fragment **9**, using Heck cross coupling. The advanced fragment **9** could be traced back from the two individual fragments, aldehyde **10** and alkyne **11**. The aldehyde **10** was commenced with D-mannitol.



Scheme 1. Retrosynthetic analysis of zeaenol and 7-*epi*-zeaenol

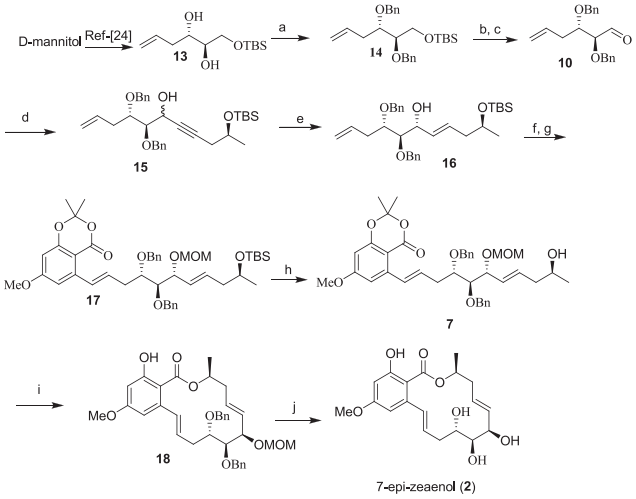
With the retrosynthetic blueprint in mind, our initial focus was on the synthesis of the alkyne fragment **11** from known aldehyde **12**. The known aldehyde **12** [22] was subjected to Ohira–Bestmann's protocol [23] with dimethyl(diazo-2-oxopropyl) phosphonate to give the propargyl alcohol **11** in 75% yield.



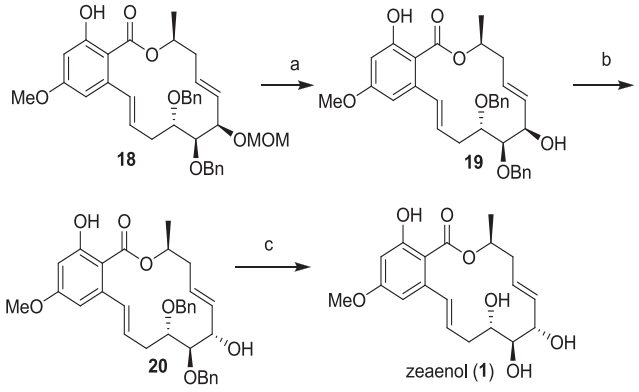
Scheme 2. Reagents and conditions. (a) K_2CO_3, MeOH, RT, 8 h, 75%.

As planned, with the requisite alkyne fragment **11** and known aromatic fragment **8** [30], the synthesis of natural product 7-*epi*-zeaenol (**2**) was accomplished from a known intermediate **13**, prepared from commercially available D-mannitol following a known protocol [24]. The dihydroxy functionality in **13** was protected as its benzyl, using benzyl bromide and NaH to afford compound **14** in 81% yield. The TBS group of **14** was deprotected smoothly using camphorsulfonic acid (CSA) in MeOH yielding a primary alcohol, which upon further treatment with Dess–Martin periodinane reagent furnished aldehyde **10** in 83% yield in two steps. Furthermore, the aldehyde **10** was coupled with alkyne **11** in an asymmetric manner following the known protocol [25-28] using Et_2Zn, $Ti(O^iPr)_4$ and (*R*)-BINOL to obtain chromatographically inseparable propargyl alcohol mixture **15**. The resulting propargyl alcohol was then reduced with $LiAlH_4$ to *trans* allyl alcohol **16** (83% yield in two steps), which was then separable by column chromatography (dr:92:08 by HPLC). The secondary allyl alcohol obtained in the $LiAlH_4$ reduction was protected as its MOM-ether using MOM-Cl and DIPEA. The resulting MOM ether was subjected to Heck cross coupling [29] with the known aromatic fragment **8** [30] using $Pd(OAc)_2$ catalyst and K_2CO_3 in DMF which resulted in the trans olefin **17** as a sole product with 88% yield in two steps. Now, the TBS deprotection of **17** was achieved smoothly with CSA in 89% yield. The macrolactonization of **7** was achieved under De Brabander's conditions [31] with NaH in 85% yield. Finally, the benzyl and MOM groups were deprotected in one-pot, by treatment of macrolactone **18** using excess $TiCl_4$ to afford the natural product, 7-*epi*-zeaenol, in 88% yield.

Synthesis of another natural product, zeaenol, commenced with compound **18**, beaing treated with TMSCl in methanol to obtain allyl alcohol **19** in 86% yield. The resulting chiral alcohol **19** was then inverted under Mitsunobu conditions [32,33] to afford alcohol **20** in 81% yield.



Scheme 3. Reagents and conditions. (a) BnBr, NaH, TBAI, THF 0 °C-rt 8 h, 81%; (b) CSA, MeOH 0 °C -rt, 12h; (c) DMP,CH_2Cl_2, rt, 3 h, 83% over two steps; (d) **11**, Et_2Zn, $Ti(O^iPr)_4$, (*R*)-BINOL, THF, rt, 12 h; (e)) $LiAlH_4$, THF 0 °C rt 12 h, 83% over two steps; (f) MOMCl, DIPEA, DMF, 0 °C-rt 12 h; (g) **8**, $Pd(OAc)_2$, Bu_4NBr, K_2CO_3, PPh_3, DMF, 80 °C, 5h, 88% over two steps (h) CSA, MeOH, rt, 1 h, 89% ; (i) NaH, THF, rt, 4 h, 85%; (j) $TiCl_4$, DCM, 0 °C-rt, 2 h, 88%.



Scheme 4. Reagents and conditions :(a) TMSCl, MeOH, 12 h, 86%; (b) (i) 4-nitrobenzoic acid, Ph_3P, DEAD, rt 12 h; (ii) K_2CO_3, MeOH, 50 °C, 10 h, 81%. over two steps; (c) $TiCl_4$, CH_2Cl_2, 2 h,0 °C, 83%.

Similarly, upon treatment of alcohol **19** using excess $TiCl_4$, the natural product zeaenol (**1**) was obtained in 83% yield.

The spectroscopic (^1H and ^{13}C NMR) and analytical data were in good agreement with the values reported values reported for the natural products [4,5].

Conclusion

In summary, we have reported a short and an efficient asymmetric total synthesis of filamentous fungi related resorcylic acid lactones 7-*epi*-zeaenol (**2**) and zeaenol (**1**) in 7 and 9 linear steps from an inexpensive known intermediate. The key steps involved in this synthesis are the Mitsunobu inversion, De Brabander's protocol for macrolactonisation, Heck cross-coupling, asymmetric alkyne aldehyde coupling, and Ohira–Bestmann alkynylation. The current methodology provides a new synthetic route with high yield and can be used further for the synthesis of various natural products of RAL's family.

Experimental Section

General remarks and methods: All reactions were performed under inert atmosphere. All glassware apparatus used for reactions were perfectly oven/flame dried. Anhydrous solvents were distilled prior to use: THF from Na and benzophenone; CH_2Cl_2, DMF from CaH_2; MeOH from Mg cake. Other commercial reagents were used without purification. Column chromatography was carried out by using silica gel (60–120 mesh) unless otherwise mentioned. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotation values were recorded on Horiba sepa 300 polarimeter given in 10^{-1} degcm^{2}g^{-1}. HRMS spectra were obtained using a TOF spectrometer. ^1H NMR and ^{13}C NMR spectra were recorded using Bruker AVANCE 300 MHz, Varian INOVA 400 MHz, and Bruker AVANCE 500 MHz spectrometers in $CDCl_3$ solution unless otherwise mentioned. The chemical shifts values are in ppm downfield from tetramethylsilane (TMS) and coupling constants (*J*) were reported in hertz (Hz). The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad.

(*S*)-*tert*-Butyldimethyl(pent-4-yn-2-yloxy)silane (11): To a stirred solution of aldehyde **13** (1.0 g, 5.3 mmol) and K_2CO_3 (2.2 g, 15.9 mmol) in methanol (30 mL), added a solution of dimethyl(diazo-2-oxopropyl) phosphonate (606 mg, 3.15 mmol) in methanol (15 mL) at room temperature and stirred for 8 hr at room temperature. Then the reaction mixture was filtered through celite and extracted with ethyl acetate (3 x 30 mL). The combined organics were washed with brine and dried over anhydrous Na_2SO_4. The solvent was removed under vacuum and the crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to afford **11** (0.78 g, 75%) as a colorless liquid. [α]D ^{25} +0.67 (c 2.5, $CHCl_3$).^1H NMR (300 MHz, $CDCl_3$)δ 3.96 (m, 1H), 2.36 (ddd, J = 16.6, 5.6, 2.7 Hz, 1H), 2.24 (ddd, J = 16.6, 7.1, 2.7 Hz, 1H), 1.98 (t, J = 2.7 Hz, 1H), 1.23 (d, J = 6.1 Hz, 3H), 0.89 (s, 9H), 0.08,(s, 3H) 0.07 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.9, 69.7, 67.5, 29.4, 25.8, 23.2, 18.1, −4.7, −4.8 ppm; HRMS (ESI): calcd for for $C_{11}H_{22}ONaSi$ [M + Na]+ 221.1333, found: 221.1337.

(((2*R*,3*S*)-2,3-Bis(benzyloxy)hex-5-en-1-yl)oxy)(*tert*-butyl)dimethylsilane (14): To a suspension of NaH (60% in mineral oil, 3.9 g,97.8 mmol) in dry THF (60 mL), added a solution of alcohol **13** (7.5 g, 32.6 mmol) in THF (50 mL) at 0 °C. After 30 min, benzyl bromide (10.0 mL, 81.5 mmol) was added slowly at 0 °C. The resulting mixture was further stirred at room temperature for 8 h and quenched with water at 0 °C and extracted with ethyl acetate (2 x 200 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to give **14** (11.2 g, 81%) as a colorless liquid. $[\alpha]_D^{25}$ −4.3 (*c* 1.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.15 (m, 10H), 5.83 (ddt, *J* = 17.1, 10.0, 7.0 Hz, 1H), 5.16 – 4.95 (m, 2H), 4.73 – 4.55 (m, 2H), 4.53 (s, 2H), 3.75 (qd, *J* = 10.8, 4.8 Hz, 2H), 3.61 (q, *J* = 5.5 Hz, 1H), 3.53 (q, *J* = 4.9 Hz, 1H), 2.38 (t, *J* = 6.3 Hz, 2H), 0.85 (s, 10H), 0.17 – 0.19 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 138.8, 135.5, 128.4, 128.1, 128.0, 127.9, 127.6, 127.6, 117.1, 80.9, 78.6, 72.9, 72.4, 62.9, 35.1,

26.1, 18.4, -5.2, -5.3; HRMS (ESI): calcd. for $C_{26}H_{39}O_3SiN$ [M + H]$^+$427.2663 found: 427.2667.

(4*S*,5*R*,6*R*,10*S*,*E*)-4,5-Bis(benzyloxy)-10-((*tert*-butyldimethylsilyl)oxy)undeca-1,7-dien-6-ol (16): Et_2Zn (17.6 mL, 17.6 mmol, 1.0 M solution) was added to a solution of alkyne **11** (3.5 g, 17.6 mmol) in toluene (20 mL) then the mixture was stirred under reflux. After 1 h the mixture was cooled to room temperature, thereafter (R)-BINOL (0.44 g, 1.6 mmol), THF (40 mL), and $Ti(OiPr)_4$ (2.6 mL, 8.8 mmol) were added to the solution. After 1 h, aldehyde **10** (2.5 g, 8.0 mmol) was added under an argon atmosphere, and the mixture was stirred for overnight at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with 1.0 M tartaric acid (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed under vacuum, which after purification by flash chromatography on silica gel (5% EtOAc/ hexanes to 20% EtOAc/ hexanes gradient), afforded mixture of propargylic alcohols **15** used in the next step without further characterization. $LiAlH_4$ (1.46 g, 12.0 mmol) was added to a stirred solution of above propargylic alcohol (8.0 mmol) in THF (30 mL) at 0 °C. The resulting solution was then stirred at RT for 12 hr. After completion of the reaction (indicated by TLC), it was cooled to 0 °C and quenched with saturated solution of Na_2SO_4 (50 mL). The solids were filtered through Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (5-10% ethyl acetate/ hexane) furnished the desired alcohol **16** (3.4 g, 83%) as a color less liquid; $[\alpha]_D^{25}$ 11.3 (*c* 1.6, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 – 7.31 (m, 10H), 6.01 – 5.68 (m, 2H), 5.59 (ddt, *J* = 15.5, 6.2, 1.3 Hz, 1H), 5.31 – 5.05 (m, 3H), 4.75 (d, *J* = 11.3 Hz, 1H), 4.70 – 4.62 (m, 2H), 4.57 (d, *J* = 11.3 Hz, 1H), 4.32 (q, *J* = 5.6 Hz, 1H), 3.92 – 3.77 (m, 1H), 3.77 – 3.69 (m, 1H), 3.54 (dd, *J* = 5.8, 4.2 Hz, 1H), 3.00 (d, *J* = 6.3 Hz, 1H), 2.51 (tdd, *J* = 7.2, 2.9, 1.4 Hz, 2H), 2.36 – 2.08 (m, 2H), 1.14 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 2.4 Hz, 9H), 0.08 (d, *J* = 1.7 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 138.0, 134.7, 131.2, 130.1, 128.5, 128.3, 128.2, 128.0, 127.8, 127.7 127.6, 127.5, 126.0, 117.4, 82.1, 79.6, 73.8, 73.7, 71.2, 68.5, 42.8, 34.8, 25.9, 23.4, 18.1, -4.5, -4.6; HRMS (ESI): calcd. for $C_{31}H_{47}O_4Si$ [M + H]$^+$ 511.3239 found: 511.3246.

5-[(*1E*,*4S*,*5S*,*6R*,*7E*,*10S*)-4,5-bis(benzyloxy)-10-((*tert*-butyldimethylsilyl)oxy)-6-(methoxymethoxy) undeca-1,7-dien-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-4-one (17): To a stirred solution of compound **16** (0.5 g, 0,95 mmol)) in DMF (10 mL) was added diisopropyl ethylamine (0.31 mL, 1.9 mmol) followed by methoxymethyl chloride (0.11 mL, 1.4 mmol) at 0 °C. The resultant mixture was stirred at room temperature for additional 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with water (20 mL) and extracted with ethyl acetate (3 x 30 mL). The combined organic layer was washed with water (2 x 50 mL) and dried over anhydrous Na_2SO_4 then removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to afford the MOM ether which was immediately used for the next reaction without further characterization.

To a stirred solution of aryl triflate **8** (0.507 g, 1.4 mmol), and the above MOM protected compound (0.95 mmol) in DMF (8 mL), $Pd(OAc)_2$ (21 mg, 0.095 mmol), Bu_4NBr (120 mg, 0.95 mmol), K_2CO_3 (262 mg, 1.9 mmol) and PPh_3 (12 mg, 0.047 mmol) were added then the mixture was degassed three times with argon under vacuum and the resultant solution was stirred at 80 °C for 5 h. After completion of the reaction (monitored by TLC), the reaction mixture was filtered through Celite and washed with water (10 mL), then extracted with ethyl acetate (3 x 20 mL). The combined organics were washed with water and dried over Na_2SO_4. The solvent was removed, and the crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to afford compound **17** (0.66 g, 88%) as a colorless oil. $[\alpha]_D^{25}$ –27.1 (*c* 1.6, $CHCl_3$);^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 15.7 Hz, 1H), 7.42 – 7.20 (m, 10H), 6.72 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 6.34 – 6.25 (m, 1H), 5.69 (ddd, *J* = 15.5, 7.7, 6.1 Hz, 1H), 5.53 (dd, *J* = 15.9, 8.2 Hz, 1H), 4.87 (d, *J* = 11.3 Hz, 1H), 4.78 – 4.72 (m, 2H), 4.64 (d, *J* = 11.4 Hz, 1H), 4.59 – 4.49 (m, 2H), 4.35 (dd, *J* = 8.2, 3.8 Hz, 1H),3.83 (s, 3H), 3.79 – 3.68 (m, 2H), 3.37 (s, 3H), 2.75 (t, *J* = 6.9 Hz, 2H), 2.22 (tq, *J* = 14.0, 7.2 Hz, 2H), 1.72 (s, 6H), 1.28 (s, 6H), 1.12 (d, *J* = 6.1 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.2, 158.7, 144.1, 138.8, 138.4, 133.0, 131.6, 130.2, 129.7, 128.5, 128.3, 128.2, 128.1, 128.0, 127.7, 127.5, 127.5, 108.3, 104.9, 103.5, 100.1, 93.4, 81.6, 78.6, 77.5, 74.0, 71.6, 68.3, 55.6, 55.6, 42.9, 33.5, 29.7, 25.9, 25.7, 25.6, 23.3, 18.1, -4.5, -4.7; HRMS (ESI): calcd. for $C_{44}H_{61}O_9NSi$ [M + H]$^+$ 761.4080, found: 761.4083.

5-[(*1E*,*4S*,*5S*,*6R*,*7E*,*10S*)-4,5-Bis(benzyloxy)-10-hydroxy-6-(methoxymethoxy)undeca-1,7-dien-1-yl)-7-methoxy-2,2-dimethyl-4*H*-benzo[d][1,3]dioxin-4-one (7): CSA (30.5 mg, 0.13 mmol) was added to a stirred solution of **17** (0.45 g, 0.1.3 mmol)) in 10 mL methanol and stirred for 1 hr at room temperature. After completion of the reaction (monitored by TLC), the solvent was removed, and the residue was dissolved in a saturated solution of $NaHCO_3$ (20 mL) and then extracted with ethyl acetate (3 x 25 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated the crude mass by silica gel column chromatography (ethyl acetate/hexane = 2:3) and

obtained **7** (340 mg, 89%) as a colorless viscous liquid. $[\alpha]_D^{25}$ –17.6 (*c* 1.0, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.52 (d, *J* = 15.8 Hz, 1H), 7.41 – 7.22 (m, 10H), 6.70 (d, *J* = 2.7 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 6.25 (dt, *J* = 15.1, 7.1 Hz, 1H), 5.62 (dd, *J* = 6.1, 3.7 Hz, 2H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.77 – 4.70 (m, 2H), 4.63 (d, *J* = 11.6 Hz, 1H), 4.58 (q, *J* = 5.9, 5.5 Hz, 1H), 4.55 – 4.48 (m, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 3.68 (d, *J* = 5.3 Hz, 2H), 3.36 (s, 3H), 2.72 (q, *J* = 7.5 Hz, 2H), 2.31 – 2.09 (m, 2H), 1.70 (s, 6H), 1.17 (d, *J* = 6.4 Hz, 3H).; ^{13}C NMR (75 MHz, $CDCl_3$) δ 164.7, 160.0, 158.7, 144.0, 138.6, 138.3, 131.9, 131.4, 130.3, 130.3, 128.3, 128.3, 128.2, 128.1, 128.0, 127.7, 127.6, 127.5, 108.3, 104.9, 100.4, 100.1, 93.9, 81.4, 78.5, 78.3, 73.9, 71.6, 67.0, 55.6, 42.1, 33.5, 25.7, 25.6, 22.8; HRMS (ESI): calcd. for $C_{38}H_{47}O_9$ $[M + H]^+$647.3215, found: 647.3211.

(3*S*,5*E*,7*R*,8*S*,9*S*,11*E*)-8,9-Bis(benzyloxy)-16-hydroxy-14-methoxy-7-(methoxymethoxy)-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (18): To a suspension of NaH (0.15 g, 3.7 mmol) washed with hexane twice to remove mineral oil and dried in dry THF (10 mL) was added a solution of alcohol **7** (0.3 g, 0.46 mmol) in THF (5 mL) at 0 °C under argon and the suspension was stirred for 5 h at room temperature. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with ice pieces at 0 °C and extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent was removed under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford **18** (0.27 mg, 85%) as a colorless liquid. $[\alpha]_D^{25}$ –55.8 (*c* 1.2, $CHCl_3$) ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 10H), 7.09 (d, *J* = 15.4 Hz, 1H), 6.38 (d, *J* = 2.5 Hz, 1H), 6.35 (d, *J* = 2.5 Hz, 1H), 5.89 (s, 1H), 5.79 (dd, *J* = 15.6, 9.3 Hz, 1H), 5.61 (ddd, *J* = 15.6, 8.1, 3.5 Hz, 1H), 5.16 – 5.07 (m, 1H), 4.76 (d, *J* = 33.0 Hz, 2H), 4.62 (t, *J* = 10.3 Hz, 1H), 4.47 (dd, *J* = 22.5, 8.9 Hz, 3H), 4.01 (m, 1H), 3.92 (m, 3H), 3.81 (s, 3H), 3.32 (s, 3H), 2.70 (dt, *J* = 18.5, 9.3 Hz, 1H), 2.65 – 2.53 (m, 3H), 2.44 – 2.27 (m, 1H), 1.42 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.7, 165.0, 164.0, 143.6, 139.0, 133.3, 132.3, 128.4, 128.2, 127.8, 127.6, 127.6, 127.3, 107.4, 99.8, 92.8, 83.6, 81.3, 78.5, 73.4, 73.2, 71.9, 55.4, 55.3, 38.7, 35.0, 29.7, 20.5; HRMS (ESI): calcd. for $C_{35}H_{41}O_8$ $[M + H]^+$589.2878, found: 589.2881.

***7-epi*-zeaenol (2):** $TiCl_4$ (1.1 mL, 1.1 mmol, 1 M in CH_2Cl_2) was added to a stirred solution of **18** (35 mg, 0.06 mmol) in CH_2Cl_2 (5 mL) at 0 °C, and the mixture was stirred for 1 hr for 30 min at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 25 mL) and washed with brine (20 mL). The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford a yellowish liquid, which was purified by silica gel column chromatography (acetone/hexane 1:1) to obtain compound **2** (17.3 mg, 88%) as a white powder. $[\alpha]_D^{25}$ –91 (*c* 1.5, MeOH); ^1H NMR (500 MHz, DMSO-d_6) δ 10.57 (s, 1H), 6.62 (d, *J* = 15.5 Hz, 1H), 6.43 (d, *J* = 2.28 Hz, 1H), 6.30 (d, *J* = 2.27 Hz, 1H), 6.1 (m, 1H), 5.66-5.53 (m, 2H), 5.19 (m, 1H), 4.82 (s, 1H), 4.80 (s, 1H), 4.50 (d, *J* = 4.1 Hz, 1H), 4.05 (m, 1H), 3.75 (s, 3H), 3.60 (m, 1H), 3.35 (m, 1H), 2.48-2.32 (m, 3H), 2.17 (m, 1H), 1.33 (d, *J* = 5.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, DMSO) δ 169.0, 161.7, 159.0, 139.6, 133.1, 132.5, 128.6, 127.0, 110.3, 102.7, 99.9, 77.5, 74.7, 72.9, 71.8, 55.2, 38.6, 36.8, 29.6, 20.4. HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$387.1415, found: 387.1419.

(3*S*,5*E*,7*R*,8*R*,9*S*,11*E*)-8,9-Bis(benzyloxy)-7,16-dihydroxy-14-methoxy-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (19): TMSCl (0.056 mL, 0.45 mmol) was added to stirred solution of **18** (0.175 mg, 0.297 mmol) in MeOH (5 mL) and allowed to stir for 2 hrs at room temperature. After completion of the reaction as indicated by TLC, the methanol was removed and the residue was dissolved in a saturated solution of $NaHCO_3$ (10 mL) then extracted with ethyl acetate (3 x 15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and then purified by silica gel column chromatography (ethyl acetate/hexane = 1:3) to give **19 (**134 mg, 86%) as a colorless liquid. $[\alpha]_D^{25}$ –76.0 (*c* 1.1, $CHCl_3$) ^1H NMR (500 MHz, C_3D_6O-d_6): 7.48-7.16 (m, 11H), 6.46 (s, 1H), 6.39 (s, 1H), 5.99 (m, 1H), 5.89 (m, 1H), 5.72 (m, 1H), 5.21 (m, 1H), 4.87-4.61 (m, 4H), 4.57 (m, 1H), 4.27 (m, 1H), 3.91-3.82 (m, 4H), 2.79 (m, 1H), 2.64-2.57 (m, 3H), 1.43 (d, *J* = 5.9 Hz, 3H) ppm; ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.6, 165.1, 164.2, 143.6, 138.9, 128.1, 128.0, 127.7, 127.5, 127.2, 106.8, 104.0, 99.7, 83.3, 78.3, 73.2, 55.0, 38.2, 19.5.HRMS (ESI): calcd. for $C_{33}H_{37}O_7$ $[M + H]^+$ 545.2534, found: 545.2541.

(3*S*,5*E*,7*S*,8*R*,9*S*,11*E*)-8,9-Bis(benzyloxy)-7,16-dihydroxy-14-methoxy-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (20): A solution of alcohol **19** (0.12 g, 0.22 mmol), *p*-nitrobenzoic acid (73 mg,0.44 mmol), and TPP (86 mg, 0.33 mmol) in THF (15 mL) at 0 °C were treated with diisopropyl azodicarboxylate (66.6 g, 0.33 mmol) and the contents were stirred at 0 °C for 1 hr and then at RT for 12 h. After completion of the reaction, the reaction mixture was concentrated, and the resulting crude material was dissolved in ethyl acetate (60 mL), and subsequently washed with the aqueous $NaHCO_3$ (30 mL), water (50 mL), dried over Na_2SO_4 and concentrated under vacuum. Purification of the residue by silica gel column chromatography (25% EtOAc in hexanes) yielded an ester which is not stable and immediately used in the next step. To a solution of above ester (0.22 mmol) in MeOH (5 mL) was added KOH (24 mg, 0.44 mmol) and the reaction

mixture is stirred for 10 hours at RT. After completion of the reaction, as indicated by TLC the solvent was removed under vacuum and the crude material was diluted with water (10 mL), then extracted with ethyl acetate (3 x 20 mL) the combined organic layer was dried over Na_2SO_4 and concentrated under the vacuum. Purification of the residue by silica gel column chromatography gave compound **20** (96 mg, 81%) as a colorless liquid. $[\alpha]_D^{25}$ –61.3 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, C_3D_6O-d_6): δ 7.50-7.13 (m, 11H), 6.47 (s, 1H), 6.40 (s, 1H), 6.10 (m, 1H), 6.00 (m, 1H), 5.81 (m, 1H), 5.31 (m, 1H), 4.97-4.45 (m, 4H), 4.34 (m, 1H), 3.95 (m, 1H), 3.90 (s, 3H), 3.66 (m, 1H), 2.65-2.47 (m, 4H), 1.44 (d, *J* = 6.2 Hz, 3H) ; ^{13}C NMR (176 MHz, $CDCl_3$) δ 171.63, 165.3, 164.2, 143.8, 139.7, 139.2, 132.2, 132.0, 131.5, 128.2, 127.8, 127.7, 127.2, 126.7, 106.8, 103.8, 99.6, 83.0, 82.0, 73.3, 72.5, 71.0, 55.0, 37.2, 34.1, 18.8; HRMS (ESI): calcd. for $C_{33}H_{37}O_7$ $[M + H]^+$545.2534, found: 545.2531.

zeaenol (1): $TiCl_4$ (1.1 mL, 1.1 mmol, 1M in CH_2Cl_2) was added to a stirred solution of **20** (30 mg, 0.05 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred for 1.45 hr at 0 °C. After completion of the reaction as indicated by TLC, the reaction mixture was quenched with a saturated solution of $NaHCO_3$ (10 mL), extracted with CH_2Cl_2 (3 x 20 mL) and washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The crude mass was that purified by silica gel column chromatography (5% methanol in chloroform) gave zeaenol (**1**) (16.6 mg, 83%) as a white powder. $[\alpha]_D^{25}$ –87 (*c* 0.9, MeOH); ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.72 (m, 1H), 7.15 (d, *J* = 15.3 Hz, 1H), 6.47 (d, *J* = 2.3, 1H), 6.42 (d, *J* = 2.3 Hz, 1H), 6.08 – 5.95 (m, 1H), 5.90 – 5.80 (m, 1H), 5.74 (dd, *J* = 15.5, 7.4 Hz, 1H), 5.36 (d, *J* = 3.6 Hz, 1H), 4.30 (d, *J* = 7.3 Hz, 1H), 4.01 (t, *J* = 6.8 Hz, 1H), 3.62 (d, *J* = 7.7 Hz, 1H), 2.61 – 2.49 (m, 3H), 2.49 – 2.41 (m, 1H), 1.49 (d, *J* = 6.2 Hz, 3H).); ^{13}C NMR (125 MHz, $CDCl_3$): δ ^{13}C NMR (126 MHz, None) δ 171.2, 165.3, 164.0, 142.9, 133.7, 131.5, 129.2, 128.5, 107.6, 103.9, 100.1, 73.1, 71.96, 71.5, 55.4, 37.8, 36.0, 29.3, 19.7; HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$387.1415, found: 387.1421

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