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Protecting-Group Directed Diastereoselective Nozaki-Hiyama-Kishi (NHK) Reaction: Total Synthesis and Biological Evaluation of Zeaenol, 7-*epi*-Zeaenol and its Analogues

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The stereoselective total synthesis of zeaenol and 7-*epi*-zeaenol was achieved in a convergent manner by using Julia-Kocienski olefination, protecting group-directed intermolecular diastereoselective Nozaki–Hiyama–Kishi (NHK) reaction, De Brabander's lactonization reaction and CBS reduction as the key steps. In this article, we have observed the most suitable protecting groups with respect to selectivity during the protecting group directed intermolecular asymmetric Nozaki-Hiyama-Kishi reaction. The Zeaenol, 7-*epi*-Zeaenol and its derivatives were analyzed for their biological activity and screened in four cancer cell lines.

Introduction

Zeaenol was first isolated and reported by Sugawara *et al.*[1] from ethyl acetate extracts of the culture fluid *Drechslera portulacae.* The relative and absolute configuration of zeaenol was confirmed by its single X-ray crystallographic and spectroscopic analysis. Later, Nicholas and co-workers reported the isolation of 15-*O*-desmethyl-(5*Z*)-7-oxozeaenol and 7-*epi*-zeaenol, along with known other resorcyclic acid lactones (RALs) (Figure 1), from filamentous fungus MSX 63935 available from leaf litter in Nigeria.[2] All these compounds exhibit potent antibacterial activity as well as mitochondrial transmembrane potential activity. The zeaenol (**1**) and 7-*epi*-zeaeneol (**2**) show similar cytotoxic activity against human tumor cell lines[3,4] and inhibition activity towards NF-κB (IC_{50} values >50 μM).

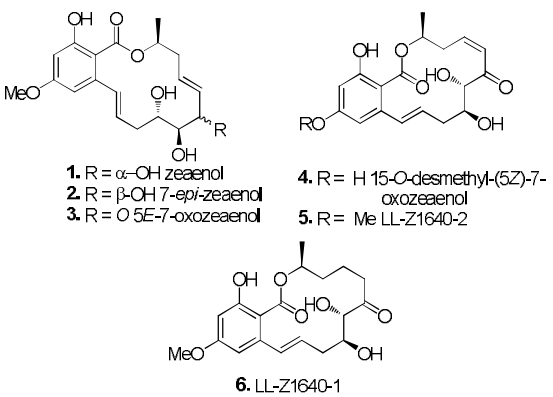


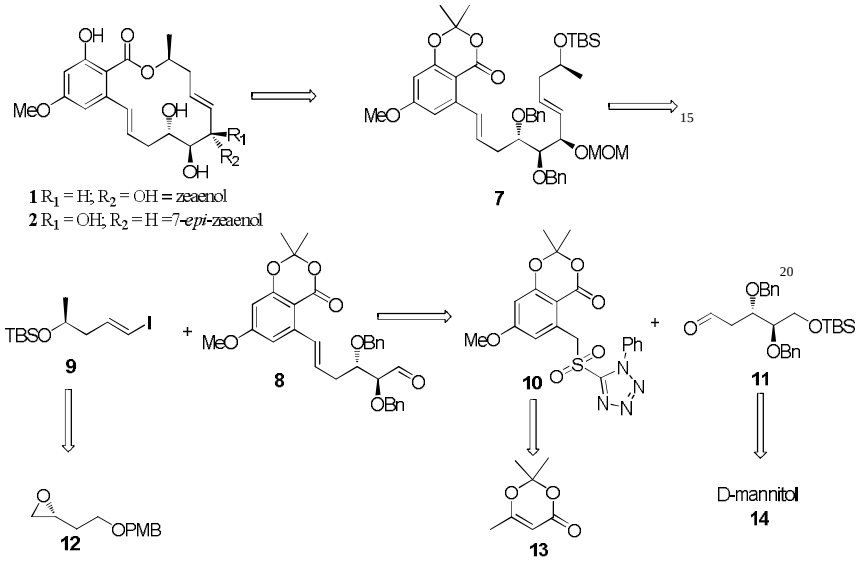
Figure 1. Structures of resorcylic acid lactones (RALs) (**1**-**6**).

The first total synthesis of zeaenol and its isopropylidine protected compound cochliomycin A were reported by Nanda *et al.*[5] using RCM strategy. Recently, Yuguo Du and co-workers[6] reported the total synthesis of zeaenol along with cochliomycin B using late stage RCM strategy. Their curious skeletal connectivities and potent biological properties attracted our attention to develop a flexible and general synthetic approach for the total synthesis of zeaenol, 7-*epi*-zeaenol whose synthesis was not reported so far and its derivatives for biological activity. As part of our ongoing research on the total synthesis of macrolides and RALs by protecting group-directed Nozaki-Hiyama-Kishi reaction as the key step.[7] In this report, we have applied the protecting group-directed diastereoselective intermolecular Nozaki-Hiyama-Kishi reaction for a convergent and concise synthesis of zeaenol and 7-*epi*-zeaenol.

Our retrosynthetic strategy of zeaenol and 7-*epi*-zeaenol is depicted in Scheme 1. The target molecule was anticipated to be derived from the macrolactonization of **7** by using De Brabander's conditions, which could be obtained by protecting group-directed intermolecular Diastereoselective Nozaki-Hiyama-Kishi reaction of **8** and **9**. The advanced fragment **8** could be prepared from **10** and **11** which in turn could be synthesized from dioxinone (**13**) and D-mannitol (**14**). The vinyl iodide fragment **9** could be derived from a known epoxide **12**.

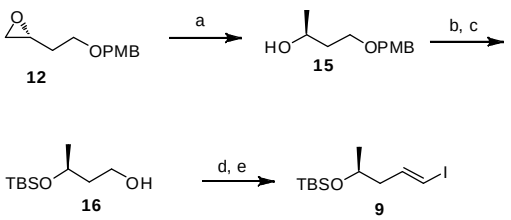
Results and Discussion

With the retrosynthetic blueprint in mind, our initial focus was on the synthesis of the iodo fragment **9**, which commenced with the known chiral epoxide **12**.[8] The epoxide **12** was prepared by using Jacobsen's hydrolytic kinetic resolution protocol.[8a] Reductive opening of epoxide **12** with $LiAlH_4$ in THF afforded alcohol **15** in 92% yield. The resulting secondary alcohol was protected as its TBS-ether[9] using TBSCl and imidazole in CH_2Cl_2



Scheme 1. Retrosynthetic approach for 7-*epi*-zeaenol (**1**) and zeaenol **(2**)

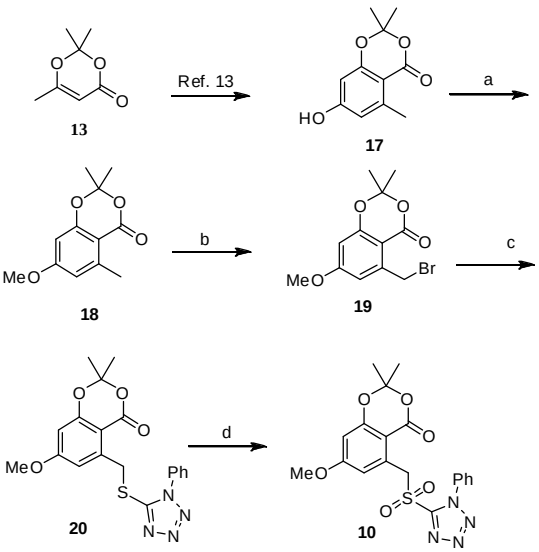
to yielded TBS protected compound, which on treatment with DDQ[10] in CH_2Cl_2/H_2O (19:1) furnished primary hydroxyl compound **16** in 88% yield over two steps. The Dess-Martin periodinane oxidation[11] of primary alcohol **16** followed by Takai olefination[12] afforded the required *trans*-vinyl iodide compound **9** (*E*/*Z* = 95:5, by NMR) in 81% yield over two steps.



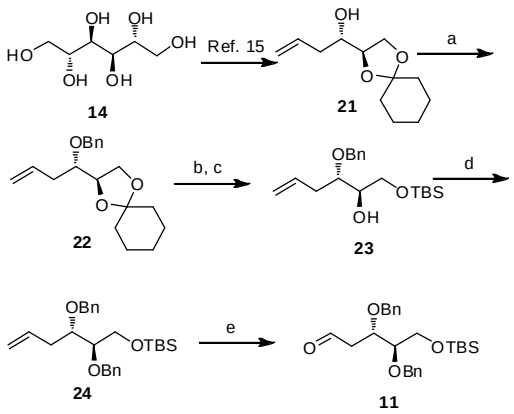
Scheme 2. Reagents and conditions: (a) LAH, THF 0 °C-rt 1 h 92%; (b) TBSCl, imidazole, CH_2Cl_2, 0 °C-rt, 10 h (c) DDQ, CH_2Cl_2/H_2O (19:1), 0 °C-rt, 2 h, 88% over two steps; (d) DMP, CH_2Cl_2, 0 °C-rt, 3 h; (e) $CrCl_2$, CHI_3, THF, rt, 16 h, 81% over two steps.

For the synthesis of another key fragment **10,** we started from **17** which was prepared from commercially available 2,2,6-trimethyl-4*H*-1,3-dioxin-4-one (**13**) by following a known protocol.[13] Subsequently protection of the phenolic hydroxyl functionality present in **17** was converted to methyl ether under Mitsunobu[14] conditions to obtain **18** in 87% yield. Bromination of benzylic position of **18** was achieved by NBS and benzoyl peroxide in CCl_4 under reflux conditions to afford benzyl bromide derivative **19** in 79% yield. Treatment of benzyl bromide derivative **19** with 1-phenyl-1*H*- tetrazole-5-thiol and Et_3N in THF gave thio-ether **20**, which was on further treatment with *m*-CPBA in CH_2Cl_2 furnished the corresponding sulfone fragment[15] **10** in 88% yield over two steps.

Synthesis of the fragment **11** was initiated from compound **21**, which was synthesized from commercially available D-mannitol following a known protocol.[16] The free hydroxyl group was protected as its benzyl ether by using benzyl bromide and NaH to give **22** in 93% yield. The deprotection of cyclohexylidene group was easily achieved by camphorsulfonic acid (CSA) in MeOH to afford diol in which the primary alcohol was selectively protected as its TBS-ether by treatment with TBS-Cl and imidazole in CH_2Cl_2 to give silyl ether compound **23** in 86% yield over two steps. The resultant secondary hydroxyl group of **23** was protected as its benzyl ether with benzyl bromide in presence of NaH to afford **24** in 91% yield. The oxidative cleavage of compound **24** under Jin's one-pot conditions using OsO_4-$NaIO_4$ and 2,6-lutidine in dioxane-water (3:1) furnished aldehyde fragment **11**[17] in 85% yield.

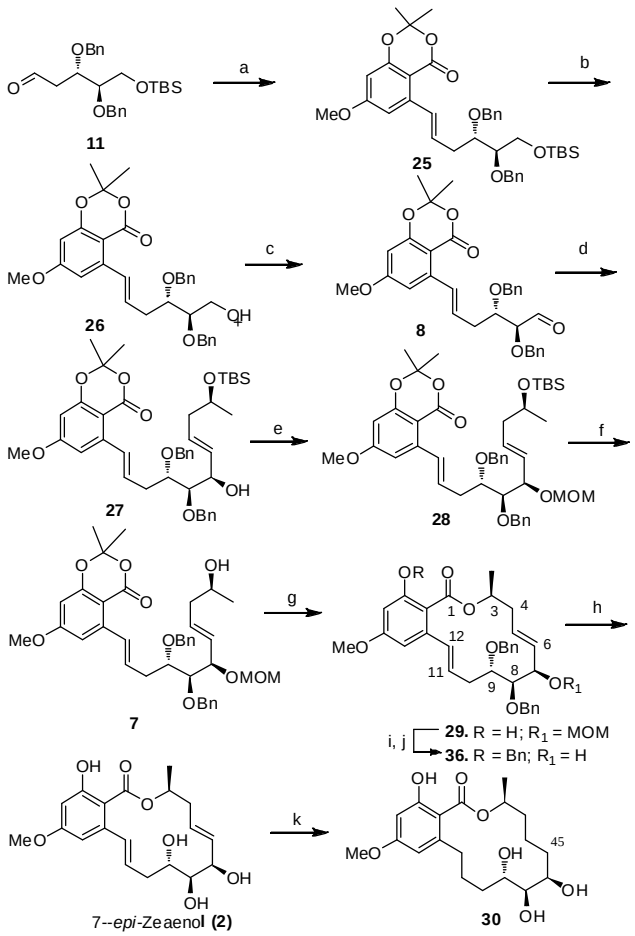


Scheme 3. Reagents and conditions: (a) MeOH, TPP, DIAD, THF, 0 °C - rt, 4 h, 87%; (b) NBS, benzoyl peroxide, CCl_4, reflux, 6 h, 79%; (c) 1-phenyl-1*H*- tetrazole-5-thiol, Et_3N, THF, reflux, 6 h; (d) *m*-CPBA, CH_2Cl_2, 0 °C-rt , 24 h, 88% over two steps.



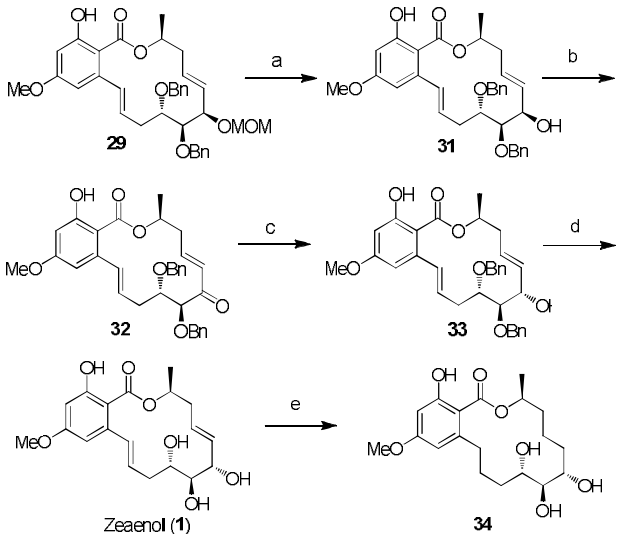
Scheme 4. Reagents and conditions: (a) BnBr, NaH, TBAI, THF 0 °C-rt, 4 h, 93%; (b) CSA, MeOH, 0-rt °C, 12 h, 90%; (c) TBSCl, Imidazole, CH_2Cl_2, 0 °C, 0.5 h, 96%; (d) BnBr, NaH, TBAI, THF, 0 °C-rt, 6 h 91%; (e) OsO_4, $NaIO_4$, 2,6-lutidine, dioxane/water (3:1), rt, 10 h, 85%.

Having both fragments **10** and **11** in hand, we procceded for Julia-Kocienski olefination[18] using KHMDS and 18-crown-6 ether in DME at –78 °C to afford desired olefin **25** exclusively in 84% yield. The TBS-ether protection in **25** was smoothly removed with CSA in MeOH to obtain **26** in 94% yield.



Scheme 5. Reagents and conditions: (a) **10**, KHMDS, 18-crown-6, DME, −78 °C, 12 h, 84%; (b) CSA, MeOH, 0 °C-rt, 0.5 h, 94%; (c) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C- rt, 3 h, 92%; (d) **9**, $CrCl_2$, $NiCl_2$, DMF, rt, 24 h, 81%; (e) MOM-Cl, DIPEA, CH_2Cl_2, 0 °C-rt, 10 h, 96%; (f) TBAF, THF, 0 °C-rt, 10 h, 91%; (g) NaH, THF, 0 °C-rt, 4 h, 78%; (h) $TiCl_4$, CH_2Cl_2, 0 °C 0.5 h, 88%; (i) NaH, BnBr, THF, 0 °C-rt, 5 h, 89%; (j) 2N HCl, THF, 15 h, 91%, (k) H_2, Pd/C, THF, rt, 24 h, 87%.

Resulting primary alcohol **26** was treated with Dess-Martin periodinane reagent to afford the corresponding aldehyde **8** in 92% yield. The aldehyde was coupled vinyl iodo fragment **9** under mild conditions using Cr(II)/Ni(II)-mediated protecting group-directed asymmetric intermolecular Nozaki-Hiyama-Kishi (NHK)[7] reaction to furnish the allyl alcohol **27** (9:1; separated by column chromatography) as a major isomer in 81% combined yield. The stereochemistry of the major isomer was ascertained by using modified Mosher's ester method at the later stage as at this stage esterification was leading to an intractable mixture of products.[19] The major isomer was taken forward towards the total synthesis of the target molecule. The secondary alcohol obtained in NHK-reaction was protected as its MOM-ether by using MOM-Cl and DIPEA to give **28** in 96% yield. The TBS group was deprotected with TBAF in THF to obtain compound **7** in 91% yield.[20] The intramolecular macrolactonization of **7** under De Brabander's conditions[21] with NaH in THF furnished the macrolactone core **29** in 78% yield. At this stage, the phenolic OH group was protected as its benzyl ether and MOM group was selectively deprotected to afford **36**. According to the modified Mosher's ester method, the free hydroxyl group present in **36** was converted to its (*R*)- and (*S*)-2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid (MTPA) ester with corresponding 2-methoxy-2-(trifluoromethyl)-2-phenylacetic acid which showed negative chemical shift differences ($\Delta\delta = \delta S - \delta R$) for protons on C8 through C12 while protons on C3 through C6 showed positive differences, which is consistent with C7 bearing an (*S*)-configuration which was in accord to the stereochemistry of 7-*epi*-zeaenol (**2**). Finally, global deprotection of benzyl and MOM groups was achieved by $TiCl_4$ to afford 7-*epi*-zeaenol (**2)** in 88% yield representing the first total synthesis of 7-*epi*-zeaenol. The spectral (^1H and ^{13}C NMR) and analytical data of 7-*epi*-zeaenol was in good agreement with the reported values.[2] To take the advantage of SAR studies, the 7-*epi*-azeaenol (**2)** was treated with Pd/C under hydrogen atmosphere to furnish tetrahydro-7-*epi*-zeaenol **30** in 87% yield.



Scheme 6. Reagents and conditions: (a) 2N HCl, THF, 12 h, 88%, (b) Dess-Martin periodinane, CH_2Cl_2, 0 °C-rt, 3 h, 90%; (c) (*S*)-CBS catalyst, $BH_3.Me_2S$, THF, −40 °C, 12 h, 82%; (d) $TiCl_4$, CH_2Cl_2, 0 °C 0.5 h, 86%; (e) H_2, Pd/C, THF, rt, 24 h, 89%.

For the synthesis of zeaenol, compound **29** was treated with 2N HCl to give secondary alcohol **31** in 88% yield. The resulting secondary hydroxy group was oxidized under Dess-Martin periodinane conditions to obtain *α,β*-unsaturated ketone **32** in 90% yield, which on asymmetric reduction using Corey-Bakshi-Shibata[22] (CBS) reagent [(*S*)-2-methyloxazaborolidine in the presence of borane-dimethylsulfide complex], provided compound **33** with required C7 stereocenter (97:3 dr, by HPLC, separated by column chromatography) in 82% yield. Deprotection of the benzyl group was achieved by treating compound **33** with excess $TiCl_4$ in CH_2Cl_2 at 0 °C to obtain zeaenol (**1**) in 86% yield. Similarly, treatment of zeaenol (**1**) with Pd/C under hydrogen atmosphere afforded tetrahydro-zeaenol (**34**) in 89% yield. The spectral (^1H and ^{13}C NMR) and analytical data of zeaenol was in accord with the reported values.[2,5,6]

The natural products zeaenol (**1**), 7-*epi*-zeaenol (**2**) and analogues **30** and **34** were tested for their cytotoxic activity and the results are summarised in Table 1.

Table 1: Cell lines were treated with different concentration of compounds for 48 h as mentioned in "materials and methods section. Cell viability was measured employing SRB assay. GI_{50}, TGI and IC_{50} (in µM) values are indicated as mean ± SD (standard deviation) of three independent experiments

code	A549			HeLa			DU 145			MDA MB 231		
	GI_{50}	TGI	IC_{50}	GI_{50}	TGI	IC_{50}	GI_{50}	TGI	IC_{50}	GI_{50}	TGI	IC_{50}
1	178 ± 2.8	368 ± 1.7	1207 ± 4.6	0.44± 0.03	84.1 ± 0.3	564 ± 3.1	33.4 ± 0.8	291 ± 1.6	738 ± 2.8	129 ± 1.2	262 ± 2.9	434 ± 1.78
2	254 ± 1.2	567 ± 2.0	1145 ± 1.5	1.0 ± 0.08	231 ± 0.95	1098 ± 4.3	0.18± 0.05	152 ± 2.1	531 ± 1.4	3.3 ± 0.09	80.2 ± 0.5	397 ± 3.1
30	8.9 ± 0.1	154± 1.52	263 ± 2.3	5.1 ± 0.05	192 ± 3.1	212 ± 1.8	23.3± 0.7	148 ± 0.9	253 ± 3.5	115 ± 1.4	195 ± 1.8	294 ± 2.14
34	1.0 ± 0.06	162 ± 2.15	241±3. 12	1.2 ± 0.06	58.4 ± 0.1	184 ± 0.84	4.2 ± 0.1	162 ± 1.48	243 ± 2.61	4.0 ± 0.07	132±2 .1	319 ± 4.1
Nocod azole	<0.0 1	0.16 ± 0.02	6.6 ± 0.1	<0.01	0.11± 0.02	5.8 ± 0.4	<0.01	0.68 ± 0.05	10.5 ± 0.3	<0.01	0.9 ± 0.01	1.3 ± 0.2

Biological studies:

In vitro cytotoxic activity:

The lead compounds inhibit the NF-kB albeit at 50µM, nevertheless we investigated their ability to inhibit growth of cancer cells. To evaluate this possibility, HeLa, A549, DU145 and MDA-MB-231 cancer cell lines were challenged with these compounds. We followed the protocol set by NCI-60 cell screen and performed the dose-response at five concentrations (0.01, 0.1,1,10 and 100 µM) of compounds. The cells were incubated. Nocodazole was employed as standard agent. Based on linear interpolation, we arrived at the values of GI_{50}, with compounds for 48 h. Nocodazole was employed as standard agent. Based on linear interpolation, we arrived at the values of GI_{50}, TGI and IC_{50}, TGI and IC_{50}. Interestingly, our anti-proliferative assays reveal that the congeners **30** and **34** demonstrate significant growth inhibition effect. In particular, **34** manifested GI_{50} of 1 µM in A549 and HeLa cells. Moreover in MDA-MB-231 and DU145 growth was inhibited at 4 µM concentrations of **34**. In contrast, **30** exhibited GI_{50} of 5 µM in HeLa cells. Similarly the GI_{50} values of **2** were at 1 µM and **1** at 0.44 µM in HeLa cells. Based on these observations, the congeners contain potent pharmacophores that elicit significant growth inhibitory response in cancer cells. Thus further delineating these pharmacophores from the molecules will possibly improve the potency of the pounds.

Conclusions

In conclusion, we have developed an efficient and concise route for the total synthesis of both zeaenol and 7-*epi*-zeaenol in convergent manner. The key steps involved in this synthesis are Takai olefination, Julia-Kocienski olefination, protecting group-directed asymmetric intermolecular Nozaki–Hiyama–Kishi (NHK) reaction, and De Brabander's lactonization. The obvious and remarkable advantages of our protocol lie in high overall yield. In addition, we identified that tetrahydro-zeaenol demonstrated significant growth inhibitory activity and these compounds are amenable for further structural modifications to improve their efficacy for anticancer therapy.

Experimental section

General Remarks: All reactions were performed under inert atmosphere, if argon mentioned. All glassware apparatus used for reactions are 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. 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 run on silica gel 60 F254 pre-coated plates (250 μm thickness). Optical rotations $[\alpha]_D$ were measured on a polarimeter and given in 10^{-1} $degcm^2g^{-1}$. Infrared spectra were recorded in $CHCl_3$/KBr (as mentioned) and reported in wave number (cm^{-1}). Mass spectral data were obtained using MS (EI) ESI, HRMS mass spectrometers. ^1H NMR spectra were recorded at 300, 400, 500 and ^{13}C NMR spectra 75, 125 MHz in $CDCl_3$ solution unless otherwise mentioned, chemical shifts are in ppm downfield from tetramethylsilane and coupling constants (*J*) are 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*)-4-(4-Methoxybenzyloxy)-butan-2-ol (15): To a stirred solution of epoxy compound **12** (2.0 g, 9.62 mmol) in THF (20 mL), was added $LiAlH_4$ (731 mg, 19.24 mmol) at 0 °C. The solution was warmed to room temperature and stirred for additional 30 min. After completion of the reaction (monitored by TLC), the reaction mixture was cooled to 0 °C and quenched with saturated solution of Na_2SO_4 (20 mL). The residue was filtered through Celite pad and the filtrate was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (ethyl acetate/ hexane = 1:9) to furnish the desired alcohol **15** (1.84 g, 92%) as a colorless liquid. $[\alpha]_D^{25}$ −4.5 (*c* 1.1, $CHCl_3$); IR (neat): 3416, 2964, 2832, 2933, 1613, 1586, 1514, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.43 (s, 2H), 3.94 (s, 3H), 3.68-3.51 (m, 2H) 2.77 (br s, 1H), 1.75-1.60 (m, 2H), 1.16 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$); δ 159.1, 129.9, 129.1, 113.6, 72.7, 68.5, 67.2, 55.1, 37.9, 23.2 ppm; HRMS (ESI): calcd. for $C_{12}H_{18}O_3Na$ $[M + 23]^+$ 233.1148, found: 233.1142.

(*S*)-3-(*tert*-Butyldimethylsilyloxy)butan-1-ol (16): To a stirred solution of alcohol **15** (1.5 g, 7.14 mmol) in CH_2Cl_2 (30 mL), was added imidazole (1.2 g, 17.85 mmol) and TBSCl (2.14 g, 14.28 mmol) at 0 °C and the reaction mixture was stirred for 30 min at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with water (30 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 2:5) to afford TBS protected compound (2.2 g, 95%) as a colorless liquid and immediately used for the next step. To a solution of above PMB ether compound (1.7 g, 5.25 mmol) in CH_2Cl_2 (38 mL) and water (2 mL) at room temperature was added DDQ (1.78 g, 7.87 mmol) and the reaction mixture was stirred for 2 h at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with saturated $NaHCO_3$ (40 mL). The organic layer was extracted with CH_2Cl_2 (2 x 50 mL) and the combined organic layer was washed with brine (60 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude mass was purified by silica gel column chromatography (ethyl acetate /hexane = 1:19) to give **16** (1.0 g, 93%) as a colorless liquid. $[\alpha]_D^{25}$ + 21.2 (*c* 1.14, $CHCl_3$); IR (neat): 3376, 2957, 2932, 2859, 1739, 1615, 1467, 1375, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.09 (m, 1H), 3.79 (m, 1H), 3.68 (m, 1H), 2.3 (br s, 1H), 1.74 (m, 1H), 1.60 (m, 1H), 1.20 (d, *J* = 6.8 Hz, 3H), 0.91 (s, 9H), 0.09 (s, 3H), 0.08 (s, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 68.3, 60.4, 40.4, 25.7, 23.4, 17.9, –4.4, –5.0 ppm; HRMS (ESI): calcd. for $C_{10}H_{22}O_2NaSi$ $[M + Na]^+$ 225.1281, found: 225.1261.

(*S*,*E*)-*tert*-Butyl(5-iodopent-4-en-2-yloxy)dimethylsilane (9): To a stirred solution of primary alcohol **16** (0.9 g, 4.41 mmol) and solid anhydrous $NaHCO_3$ (1.0 g) in CH_2Cl_2 (25 mL) was added Dess–Martin periodinane (4.0 g, 6.65 mmol) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 3 h. After completion of the reaction (monitored by TLC), the mixture was filtered through a bed of Celite. The filtrate was washed with saturated $NaHCO_3$ (2 x 25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude mass over silica gel column chromatography (ethyl acetate/hexane = 1:25) to afford corresponding aldehyde (0.82 g, 93%) as a pale-yellow liquid which was immediately used for next step. To a stirred suspension of $CrCl_2$ (2.89 g, 23.76 mmol) in THF (25 mL) was added the above aldehyde (0.8 g, 3.96 mmol) and CHI_3 (4.67 g, 11.88 mmol) dissolved in THF (25 mL) at ambient temperature. The reaction mixture was protected from light and stirred at ambient temperature for 16 h. After completion of the reaction (monitored by TLC), the green reaction mass was quenched with water (30 mL). The reaction mixture was extracted with ethyl acetate (3 x 40 mL). The combined organic extract was washed with saturated aqueous $Na_2S_2O_3$ (2 x 50 mL) followed by brine (50 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane) afforded **9** (1.12 g, 87%) as a pale-yellow oil. $[\alpha]_D^{25}$ +9.7 (*c* 1.5, $CHCl_3$); IR (neat): 2955, 2928, 2856, 1607, 1464, 1375, 1253 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.48 (m, 1H), 6.02 (dd, *J* = 14.4, 1.5 Hz, 1H), 3.83 (m, 1H), 2.17-2.11 (m, 2H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.6, 76.5, 67.5, 45.9, 25.8, 23.5, 18.1, –4.6,–4.7 ppm.

7-Methoxy-2,2,5-trimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (18): Compound **17** (3.5 g, 16.83 mmol) was taken in THF (40 mL) and MeOH (1.0 mL, 25.25 mmol) was added followed by Ph_3P (6.6 g, 25.25 mmol) at 0 °C. After being stirred for 5 minutes at the same temperature, diisopropyl azodicarboxylate (4.9 mL, 25.25 mmol) was added drop wise to the reaction mixture and stirred for an additional 4 h at room temperature. The reaction mixture was concentrated under reduced pressure and purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to obtain **18** (3.2 g, 87%) as a white solid. Mp = 147−149 °C; IR (neat): 2927, 2852, 1730, 1614, 1559, 1454, 1205, 1160 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.41 (d, *J* = 2.3 Hz, 1H), 6.23 (d, *J* = 2.3 Hz, 1H), 3.82 (s, 3H), 2.63 (s, 3H), 1.69 (s, 6H) ppm; ^{13}C

NMR (75 MHz, $CDCl_3$): δ 164.7, 160.4, 158.8, 145.3, 112.7, 104.9, 99.2, 98.1, 55.4, 25.6, 22.2 ppm; HRMS (ESI): calcd. for $C_{12}H_{14}O_4Na$ $[M + Na]^+$ 245.0784, found: 245.0803.

5-(Bromomethyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3] dioxin-4-one (19): To a solution of **18** (3.0 g, 13.51 mmol) in CCl_4 (40 mL) was added NBS (1.3 g, 7.43 mmol) followed by benzoyl peroxide (40 mg) and the reaction mixture heated under reflux. After 3 h, another portion of NBS (1.3 g, 7.43 mmol) and benzoyl peroxide (40 mg) was added to the above reaction mixture and heated under reflux condition for an additional 3 h. The reaction was cooled to room temperature, the solid succinimide filtered off and the solvent removed under reduced pressure. The resulting orange oil was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to afford compound **19** (3.18 g, 79%) as a white solid. Mp = 89−92 ºC; IR (neat): 2992, 2920, 2850, 1728, 1612, 1580, 1435, 1205, 1163 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.69 (s, 1H), 6.37 (s, 1H), 4.96 (s, 2H), 3.83 (s, 3H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 159.6, 159.2, 143.3, 113.5, 105.5, 101.4, 98.2, 55.8, 31.1, 25.5 ppm; HRMS (ESI): calcd. for $C_{12}H_{14}O_4Br$ $[M + H]^+$ 301.0070 found, 301.0065.

7-Methoxy-2,2-dimethyl-5-((1-phenyl-1*H*-tetrazol-5-ylthio) methyl)-4*H*-benzo[*d*][1,3]dioxin-4-one (20): To a stirred solution of 1-phenyl-1*H*-tetrazole-5-thiol (2.2 g,12.9 mmol) in dry THF (30 mL), was added Et_3N (1.74 mL, 12.9 mmol) and the mixture was stirred at room temperature. After 40 min, compound **19** (2.6 g, 8.67 mmol) was added and the reaction mixture was refluxed for 6 h. The reaction mixture was diluted with water (30 mL) and extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give the crude thioether which was purified by flash chromatography (ethyl acetate/hexane = 1:7) to afford compound **20** (3.3 g, 96%) as a white solid. Mp. = 144−146 ºC; IR (neat): 3068, 3000, 2924, 2853, 1717, 1611, 1579, 1499, 1386, 1289 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.59−7.45 (m, 5H), 7.13 (d, *J* = 2.5 Hz, 1H), 6.33 (d, *J* = 2.5 Hz, 1H), 4.96 (s, 2H), 3.87 (s, 3H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.1, 160.6, 159.0, 154.8, 142.7, 133.5, 129.9,129.7, 123.7, 113.5, 105.6, 103.6, 101.6, 55.8, 35.8, 25.5 ppm; HRMS (ESI): calcd. for $C_{19}H_{19}O_4N_4S$ $[M + H]^+$ 399.1121, found: 399.1124.

(7-Methoxy-2,2-dimethyl-5-((1-phenyl-1*H*-tetrazol-5-ylsulfonyl)methyl)-4*H*-benzo[*d*][1,3]dioxin -4-one (10): *m*-CPBA (70% w/w) (4.1 g, 23.73 mmol) was added in small portions to a solution of the thioether **20** (2.7 g, 6.78 mmol) in CH_2Cl_2 (30 mL) at 0 °C and the reaction mixture was stirred at room temperature for 24 h. Then it was quenched with saturated Na_2SO_3 solution (30 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was washed with saturated $NaHCO_3$ solution (75 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:6) to afford compound **10** (2.7 g, 92%) as a light yellow solid. Mp. = 102–104 °C; IR (neat): 3074, 2999, 2926, 2854, 1720, 1613, 1582, 1355, 1291cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.68−7.49 (m, 5H), 6.80 (d, *J* = 2.5 Hz, 1H), 6.45 (d, *J* = 2.5 Hz, 1H), 5.63 (s, 2H), 3.86 (s, 3H), 1.68 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.8, 160.6, 159.2, 153.2, 132.9, 131.2, 130.1, 129.3, 125.6, 116.1, 106.0, 105.7, 102.7, 59.2, 55.8, 25.4 ppm; HRMS (ESI): calcd. for $C_{19}H_{18}O_6N_4SNa$ $[M + Na]^+$ 453.0839, found: 453.0839.

(*R*)-2-((*S*)-1-(Benzyloxy)but-3-enyl)-1,4-dioxaspiro[4.5]decane (22): To a suspension of NaH (60% in mineral oil, 2.83 g, 70.75 mmol) in dry THF (60 mL), was added alcohol **21** (7.5 g, 35.37 mmol) in THF (30 mL) at 0 °C. The suspension was stirred for 1 h at room temperature. The benzyl bromide (4.2 mL, 35.37 mmol) was added slowly to the above reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for additional 4 h and quenched with water at 0 °C. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine solution (100 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to give **22** (9.93g, 93%) as a light-yellow liquid. $[\alpha]_D^{25}$ +16.7 (*c* 1.15, $CHCl_3$); IR (neat): 3343, 3069, 3033, 2936, 2861, 1723, 1450, 1160, 698 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.31-7.21 (m, 5H), 5.86 (m, 1H), 5.15-5.03 (m, 2H), 4.59 (q, *J* = 11.3 Hz, 2H), 4.04-3.94 (m, 2H), 3.82 (m, 1H), 3.51 (m, 1H), 2.47-2.26 (m, 2H), 1.63-1.52 (m, 8H), 1.43-1.35 (m, 2H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.3, 134.2, 128.3, 127.7, 127.5, 117.4, 109.5, 78.9, 76.7, 72.4, 66.0, 36.3, 35.6, 34.8, 25.1, 23.9, 23.8 ppm; HRMS (ESI): calcd. for $C_{19}H_{27}O_3$ $[M + H]^+$ 303.1954 found: 303.1954.

(2*R*,3*S*)-3-(Benzyloxy)-1-(*tert*-butyldimethylsilyloxy)hex-5-en-2-ol (23): To a stirred solution of **22** (9.0 g, 29.8 mmol) in MeOH (20 mL) was added CSA (0.28 g, 2.98 mmol) at 0 °C and the reaction mixture was stirred for 12 h at rt. After completion of the reaction (monitored by TLC), it was quenched with saturated solution of $NaHCO_3$ (100 mL) and MeOH was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 150 mL) and the combined organic layer was washed with brine (150 mL), dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:1) furnished the desired diol (5.95 g, 90%) as a viscous colorless liquid that was immediately used for next step. To a stirred solution of above diol (5.5 g, 24.77 mol) in CH_2Cl_2 (60 mL), was added imidazole (1.85 g, 27.25 mmol) and TBSCl (3.71 g, 24.77 mmol) at 0 °C and the reaction was stirred for 30 min at the same temperature. After completion of the reaction (monitored by TLC), it was quenched with water (50 mL) and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 2:5) to afford **23** (7.75 g, 96%) as a colorless liquid. $[\alpha]_D^{25}$ +15.9 (*c* 1.0, $CHCl_3$); IR (neat): 3343, 3069, 2936, 2861, 1723, 1450, 1278 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36-7.31 (m, 5H), 5.94 (m, 1H), 5.21-5.06 (m, 2H), 4.65 (d, *J* = 11.0 Hz, 1H), 4.52 (d, *J* = 11.0 Hz, 1H), 3.77 (q, *J* = 6.6 Hz, 1H), 3.72-3.66 (m, 2H), 3.53 (q, *J* = 6.6 Hz, 1H), 2.54-2.39 (m, 2H), 0.91 (s, 9H), 0.08 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.4, 134.7, 128.3, 127.8, 127.6, 117.2, 78.7, 72.4, 72.1, 63.6, 34.7, 25.8, 18.2, –5.4 ppm; HRMS (ESI): calcd. for $C_{19}H_{32}O_3NaSi$ $[M + Na]^+$ 359.2012, found: 359.2010.

2*R*,3*S*)-2,3-Bis(benzyloxy)hex-5-enyloxy)(*tert*-butyl)dimethyl silane (24): To a suspension of NaH (60% in mineral oil, 1.6 g, 40.07 mmol) in dry THF (40 mL), was added alcohol **23** (6.85 g, 20.38 mmol) in THF (30 mL) at 0 °C. The suspension was stirred for 1 h at room temperature. The benzyl bromide (3.6 mL, 30.57 mmol) was added slowly to the above reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for 4 h and quenched with water at 0 °C. The reaction mixture was extracted with ethyl acetate (2 x 100 mL). The combined organic layer was washed with brine solution (75 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to give **24** (7.9 g, 91%) as a light-yellow liquid. $[\alpha]_D^{25}$ –2.1 (*c* 1.3, $CHCl_3$); IR (neat): 3066, 3032, 2953, 2858, 1732, 1641, 1458, 1254 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.42-7.23 (m, 5H), 5.88 (m, 1H), 5.15-5.01 (m, 2H), 4.78-4.55 (m, 4H), 3.87-3.74 (m, 2H), 3.66 (m, 1H), 3.59 (m, 1H), 2.43 (t, *J* = 6.0 Hz, 2H), 0.96 (s, 9H), 0.05 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.7, 138.5, 135.2, 128.1, 127.7, 127.6, 127.4, 127.3, 116.8, 80.7, 78.4, 72.6, 72.1, 62.7, 34.9, 25.9, 18.2, –5.4 ppm; HRMS (ESI): calcd. for $C_{26}H_{38}O_3NaSi$ $[M + Na]^+$ 449.2482 found: 449.2469.

5-((4*S*,5*R*,*E*)-4,5-Bis(benzyloxy)-6-(*tert*-butyldimethylsilyloxy) hex-1-enyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (25): To a stirred solution of the compound **24** (2.2 g, 5.16 mmol) in 1,4-dioxane (25 mL) was added 2,6–lutidine (2.4 mL, 20.64 mmol) and $NaIO_4$ (4.78 g, 20.64 mmol) in water (10 mL) followed by OsO_4 (0.51 mL, 0.51 mmol, 1 M solution in toluene) at room temperature. The reaction mixture was stirred under dark at room temperature for 6 h. After completion of the reaction (monitored by TLC), it was quenched with saturated aq. Na_2SO_3 (30 mL) solution. Organic solvent was removed under reduced pressure and the residual aqueous layer was extracted with ethyl acetate (3 x 75 mL). The combine organic layers was washed with brine (2 x 30 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a colorless oil which was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to obtain aldehyde **11** (1.88 g, 85%) as a colorless liquid which was immediately used for next step without further purification and characterization. To a stirred solution of **10** (2.36 g, 5.5 mmol) and 18-crown-6 (2.1 g, 8.2 mmol) in DME (25 mL) was added KHMDS (0.5 M in toluene, 11.0 mL, 5.5 mmol) at –78 °C. After 20 min, a solution of **11** (1.57 g, 3.67 mmol) in DME (6 mL) was added and the mixture was stirred at –78 °C for 1 h. The reaction mixture was gradually warmed to –10 °C. After being stirred overnight at –10 °C, the mixture was quenched with saturated NH_4Cl (30 mL) and extracted with ethyl acetate (3 x 50 mL). The extract was washed with brine (75 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to give **25** (1.94 g, 84%) as a colorless oil. $[\alpha]_D^{25}$ −12.5 (*c* 1.65, $CHCl_3$); IR (neat); 2928, 2854, 1728, 1607, 1572, 1278, 1159, 1097, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 15.9 Hz, 1H), 7.37-7.22 (m, 10H), 6.68 (d, *J* = 3.0 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 6.23 (m, 1H), 4.82-4.45 (m, 4H), 3.87 (dd, *J* = 10.6, 3.8 Hz, 1H), 3.81 (s, 3H), 3.76 (m, 1H), 3.69-3.49 (m, 2H), 2.65 (t, *J* = 6.0 Hz, 1H), 2.58 (t, *J* = 6.0 Hz, 1H), 1.69 (s, 6H), 0.90 (s, 9H), 0.06 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.6, 160.1, 158.6, 143.9, 138.6, 131.6, 130.1, 129.9, 128.2, 127.9, 127.8, 127.5, 127.4, 108.2, 104.8, 100.1, 80.8, 78.5, 72.7, 72.1, 62.8, 55.5, 34.1, 25.9, 25.6, 25.6, 18.2, –5.4 ppm; HRMS (ESI): calcd. for $C_{37}H_{48}O_7NaSi$ $[M + Na]^+$ 655.3061, found: 655.3065.

5-((4*S*,5*R*,*E*)-4,5-Bis(benzyloxy)-6-hydroxyhex-1-enyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (26): To a stirred solution of compound **25** (1.45 g, 2.29 mmol) in MeOH (20 mL) was added camphorsulfonic acid (53 mg, 0.229 mmol) at 0 °C and the resulting solution was stirred for 0.5 h at ambient temperature. After completion of the reaction (monitored by TLC), mixture was quenched with aqueous $NaHCO_3$ (20 mL) and MeOH was removed under reduced pressure. The residue was extracted with ethyl acetate (3 x 50 mL) and the combined organic layer was washed with brine (75 mL) and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and purification of the crude product by silica gel column chromatography (ethyl acetate/hexane = 1:4) furnished alcohol **26** (1.12 g, 94%) as a colorless liquid. $[\alpha]_D^{25}$ −4.5 (*c* 0.7, $CHCl_3$); IR (neat) 3443, 2989, 2929, 1723, 1606, 1575, 1453, 1361, 1281 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, *J* = 15.9 Hz, 1H), 7.38-7.25 (m, 10H), 6.68 (d, *J* = 2.3 Hz, 1H), 6.35 (d, *J* = 2.3 Hz, 1H), 6.17 (m, 1H), 4.73-4.60 (m, 4H), 3.86-3.76 (m, 6H), 3.63-3.57 (m, 1H), 2.71-2.64 (m, 2H), 1.70 (s, 6H) ppm; ^{13}C NMR (75MHz, $CDCl_3$): δ 164.7, 160.1, 158.6, 143.7, 138.0, 130.9, 130.3, 128.4, 127.9, 127.7, 127.6, 108.4, 104.9,103.6, 100.1, 79.9, 78.7, 72.1, 61.2, 55.8, 34.3, 25.6, 25.5 ppm; HRMS (ESI): calcd. for $C_{31}H_{35}O_7$ $[M + H]^+$ 519.2377, found: 519.2364.

5-((1*E*,4*S*,5*R*,6*R*,7E,10*S*)-4,5-Bis(benzyloxy)-10-(*tert*-butyldimethylsilyloxy)-6-hydroxyundeca-1,7-dienyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (27): A solution of primary alcohol **26** (1.05 g, 2.03 mmol) and solid anhydrous $NaHCO_3$ (0.26 g, 3.12 mmol) in CH_2Cl_2 (30 mL) at 0 °C, was added Dess–Martin periodinane (1.2 g, 3.04 mmol). The resulting reaction mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), the mixture was filtered through Celite bed and the filtrate was washed with saturated $NaHCO_3$ (2 x 20 mL). The organic layer was separated and extracted with CH_2Cl_2 (2 x 50 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the organic layer was removed under reduced pressure. Purification of the crude reaction mass by flash chromatography (ethyl acetate/hexane = 1:10) afforded the corresponding aldehyde **8** (0.96 g, 92%) as a pale-yellow liquid that was immediately used for next step. Mixture of anhydrous $CrCl_2$ (2.9 g, 18.5 mmol) and $NiCl_2$ (238 mg, 1.85 mmol) was added to a mixture of aldehyde **8** (0.95 g, 1.85 mmol) and vinyl iodide **9** (1.2 g, 3.7 mmol) in degassed DMF (10 mL + 5 mL rinse twice) at ambient temperature. The resultant mixture was stirred at ambient temperature for 24 h. The reaction was quenched with saturated NH_4Cl (50 mL) at 0 °C. The resultant solution was stirred at room temperature for 15 min and mixture was extracted with diethyl ether (3 x 50 mL). The organic layer was washed with brine (100 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. Purification of the residue by silica gel column chromatography (ethyl acetate/hexane = 1:7) furnished **27** (0.9 g, 81%), as colorless liquid. $[\alpha]_D^{25}$ +2.1 (*c* 1.2, $CHCl_3$); IR

(neat): 3448, 2925, 2854, 1725, 1606, 1575, 1458, 1378, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 15.9 Hz, 1H), 7.39-7.29 (m, 10H), 6.70 (d, *J* = 3.0 Hz, 1H), 6.34 (d, *J* = 3.0 Hz, 1H), 6.26 (m, 1H), 5.81-5.61 (m, 2H), 4.75-4.59 (m, 4H), 4.35 (m, 1H), 3.86-3.72 (m, 5H), 3.59 (m, 1H), 2.82-2.65 (m, 2H), 2.35 (t, *J* = 7.6 Hz, 2H), 1.70 (s, 6H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.88 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): 164.8, 160.2, 158.7, 143.9, 138.3, 137.9, 131.1, 130.9, 130.7, 130.0, 128.4, 128.3, 128.0, 127.9, 127.7, 127.6, 108.4, 104.9, 103.6, 100.1, 82.1, 79.8, 74.0, 73.8, 71.7, 68.5, 55.6, 42.8, 33.7, 29.7, 25.8, 25.6, 23.4, 18.1, –4.6, –4.7 ppm; HRMS (ESI): calcd. for $C_{42}H_{56}O_8NaSi$ $[M + Na]^+$ 739.3636, found: 739.3639.

5-((1*E*,4*S*,5*S*,6*R*,7*E*,10*S*)-4,5-Bis(benzyloxy)-10-(*tert*-butyl dimethylsilyloxy)-6-(methoxy methoxy)undeca-1,7-dienyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (28): To a stirred solution of compound **27** (0.855 g, 1.19 mmol)) in CH_2Cl_2 (20 mL), was added diisopropyl ethylamine (0.63 mL, 3.5 mmol) and stirred for 30 min at 0 °C under argon atmosphere. Methoxymethyl chloride (0.23 mL, 2.98 mmol) was added to the above reaction mixture in CH_2Cl_2 (10 mL) at same temperature. The resultant mixture was stirred at room temperature for additional 10 h. After completion of the reaction (monitored by TLC), it was quenched with water (20 mL) and extracted with CH_2Cl_2 (3 x 30 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:20) to afford MOM ether **28** (0.87 g, 96%) as a colorless oil. $[\alpha]_D^{25}$ −25.1 (*c* 1.2, $CHCl_3$); IR (neat): 2925, 2854, 1729, 1604, 1575, 1457, 1277, 1156, 1032, 833, 774 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, *J* = 15.9 Hz, 1H), 7.39-7.22 (m, 10H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.33 (d, *J* = 2.3 Hz, 1H), 6.28 (m, 1H), 5.66 (m, 1H), 5.51 (dd, *J* = 15.9, 8.31 Hz, 1H), 4.86 (d, *J* = 11.3 Hz, 1H), 4.77-4.48 (m, 5H), 4.33 (dd, *J* = 8.3, 3.8 Hz, 1H), 3.87-3.80 (m, 4H), 3.78-3.65 (m, 2H), 3.36 (s, 3H), 2.79-2.69 (m, 2H), 2.36-2.11 (m, 2H), 1.69 (s, 6H), 1.10 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 9H), 0.04 (s, 6H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 160.1, 158.6, 144.0, 138.7, 138.4, 132.9, 131.6, 130.1, 128.5, 128.3, 128.2, 128.0, 127.9, 127.7, 127.5, 127.4, 108.2, 104.9, 103.6, 100.1, 93.3, 81.5, 78.6, 77.5, 73.9, 71.5, 68.3, 55.6, 55.5, 42.9, 33.5, 25.8, 25.7, 25.5, 23.2, 18.1, –4.6, –4.8 ppm; HRMS (ESI): calcd. for $C_{44}H_{60}O_9NaSi$ $[M + Na]^+$ 783.3898, found: 783.3890.

5-((1*E*,4*S*,5*S*,6*R*,7*E*,10*S*)-4,5-Bis(benzyloxy)-10-hydroxy-6-(methoxymethoxy)undeca-1,7-dienyl)-7-methoxy-2,2-dimethyl-4*H*-benzo[*d*][1,3]dioxin-4-one (7): To a stirred solution of **28** (0.805 g, 1.08 mmol)) in dry THF (20 mL) was added TBAF (1 M in THF, 1.62 mL, 1.62 mmol) at 0 °C. The resulting mixture was stirred for an additional 10 h at room temperature. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 x 30 mL) and washed with brine (50 mL).The organic layer was dried over anhydrous Na_2SO_4 and concentrated to afford a yellowish liquid. Purification of the above crude mass by silica gel column chromatography (ethyl acetate/hexane = 2:3) furnished **7** (654 mg, 91%) as a colorless viscous liquid. $[\alpha]_D^{25}$ −19.1 (*c* 1.5, $CHCl_3$); IR (neat); 3435, 2956, 2926, 2855, 1727, 1608, 1578, 1453, 1283 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.53 (d, *J* = 16.1 Hz, 1H), 7.38-7.22 (m, 10H), 6.69 (d, *J* = 3.0 Hz, 1H), 6.33 (d, *J* = 2.7 Hz, 1H), 6.24 (m, 1H), 5.63-5.60 (m, 2H), 4.84 (d, *J* = 11.1 Hz, 1H), 4.77-4.49 (m, 5H), 4.33 (m, 1H), 3.82 (s, 3H), 3.76 (m, 1H), 3.71-3.65 (m, 2H), 3.35 (s, 3H), 2.77-2.66 (m, 2H), 2.27-2.11 (m, 2H), 1.69 (s, 6H), 1.17 (d, *J* = 6.0 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.7, 160.1, 158.6, 143.9, 138.3, 131.8, 131.3, 130.3, 130.2, 128.3, 128.2, 128.0, 127.5, 127.5, 127.3, 108.3, 104.9, 100.1, 93.7, 81.4, 78.5, 78.2, 73.9, 71.5, 66.9, 55.5, 42.0, 33.4, 25.6, 25.5, 22.8 ppm; HRMS (ESI): calcd. for $C_{38}H_{46}O_9$ Na $[M + Na]^+$ 669.3034, found: 669.3034.

(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 (29): To a suspension of NaH (0.256 g, 6.4 mmol, NaH was washed with hexane twice to remove mineral oil and dried) in dry THF (10 mL), was added alcohol **7** (0.515 g, 0.8 mmol) in THF (5 mL) at 0 °C under argon atmosphere and the suspension was stirred for 4 h at room temperature. After completion of the reaction (monitored by TLC), it was quenched with ice pieces at 0 °C. The organic layer was separated and the aqueous layer extracted with ethyl acetate (3 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and solvent removed under reduced pressure. The crude mass was purified by silica gel column chromatography (ethyl acetate/hexane = 1:9) to afford **29** (366 mg, 78%) as a colorless liquid. $[\alpha]_D^{25}$ −49.2 (*c* 1.7, $CHCl_3$); IR (neat): 2923, 2853, 1729, 1647, 1608, 1572, 1458, 1378, 1256 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.71 (s, 1H), 7.31-7.20 (m, 10H), 7.09 (d, *J* = 15.8 Hz, 1H), 6.38 (br s, 1H), 6.35 (d, *J* = 2.9 Hz, 1H), 5.89 (m, 1H), 5.79 (m, 1H), 5.61 (m, 1H), 5.12 (m, 1H), 4.80 (s, 2H), 4.63 (d, *J* = 6.9 Hz, 1H), 4.52-4.43 (m, 3H), 4.02 (m, 1H), 2.92 (m, 1H), 3.81 (s, 3H), 3.30 (s, 3H), 2.75-2.56 (m, 3H), 2.37 (m, 1H), 1.42 (d, *J* = 6.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 164.9, 163.9, 143.5, 138.9, 138.3, 133.2, 132.2, 128.3, 128.1, 127.7, 127.5, 127.2, 107.3, 104.1, 99.7, 92.7, 83.6, 81.3, 78.4, 73.4, 73.1, 71.8, 55.4, 55.3, 38.6, 34.9, 20.5 ppm; HRMS (ESI): calcd. for $C_{35}H_{40}O_8Na$ $[M + Na]^+$ 611.2615, found: 611.2611.

7-*epi*-Zeaenol (2): To a stirred solution of **29** (50 mg, 0.09 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.8 mL, 1.8 mmol, 1 M in CH_2Cl_2) at 0 °C, and the mixture was stirred for 30 min at 0 °C. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (2 x 10 mL) and washed with brine (15 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** (28 mg, 88%) as a white powder. $[\alpha]_D^{25}$ −87 (*c* 1.2, MeOH); IR (neat): 3424, 2926, 2854, 2738, 2489, 1607, 1637, 1385, 1254 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.56 (s, 1H), 6.64 (d, *J* = 15.8 Hz, 1H), 6.43 (d, *J* = 2.2 Hz, 1H), 6.31 (d, *J* = 2.2 Hz, 1H), 6.09 (m, 1H), 5.67-5.52 (m, 2H), 5.10 (m, 1H), 4.84 (s, 1H), 4.79 (s, 1H), 4.48 (d, *J* = 3.9 Hz, 1H), 4.05 (m, 1H), 3.74 (s, 3H), 3.58 (m, 1H), 3.45 (m, 1H), 2.48-2.31 (m, 3H), 2.17 (m, 1H), 1.31 (d, *J* = 5.9 Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.9, 161.6, 158.8, 139.5, 132.9, 132.4, 128.5, 126.9, 110.2, 102.6, 99.8, 77.4, 74.6, 72.8, 71.7, 55.2, 38.5, 36.7, 20.0 ppm; HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$ 387.1417, found: 387.1405.

1,2,7,8-Tetrahydro-7-*epi*-zeaenol (30): The compound **2** (15

mg, 0.04 mmol) was in MeOH (5 mL) and commercial Pd/C (10 mg, 10% w/w) was added in one portion. The resulting suspension was stirred under an atmosphere of H_2 for 24 h until complete disappearance of starting material occurred (indicated by TLC). The suspension was filtered through Celite pad and washed with ethyl acetate (10 mL). The combined filtrates were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (acetone/hexane = 1:1) to afford 2,7,8-tetrahydro-7-*epi*-Zeaenol (12 mg, 87%) as white power .$[\alpha]_D^{25}$ −15.6 (*c* 1.2 $CHCl_3$); IR (neat): 3375, 2924, 2853, 1743, 1628, 1591, 1258 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ 10.16 (s, 1H), 6.32 (s, 1H), 6.26 (s, 1H), 5.03 (m, 1H), 4.42 (d, *J* = 4.5 Hz, 1H), 4.31 (d, *J* = 4.5 Hz, 1H), 4.21 (s, 1H), 4.01 (s, 1H), 3.71 (s, 3H), 3.58 (m, 1H), 3.40 (m, 2H), 3.07 (m, 1H), 2.61 (m, 2H), 1.71-1.27 (m, 8H), 1.25 (d, *J* = 5.6 Hz, 3H) ppm; ^{13}C NMR (125 MHz, DMSO-d_6): δ 168.5, 161.0, 157.8, 143.3, 113.0, 105.9, 98.7, 77.6, 71.4, 71.1, 70.5, 54.9, 45.6, 35.0, 32.3, 32.1, 32.0, 27.5, 21.1, 20.4 ppm; HRMS (ESI): calcd. for $C_{19}H_{28}O_7Na$ $[M + Na]^+$ 391.1732, found: 391.1721.

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 (31): A solution of compound **29** (200 mg, 0.34 mmol) in THF (5 mL) was treated with 2N HCl (5 mL) and allowed to stirred for 15 h at room temperature. After completion of the reaction (monitored by TLC) ethyl acetate (5 mL) and H_2O (5 mL) were added. The layers were separated and the aqueous phase extracted with ethyl acetate (2 x 10 mL). The combined organic portion was washed with saturated sodium bicarbonate solution (2 x 15 mL) followed by brine solution (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:6) to give **32 (**162 mg, 88%) as a colorless liquid. $[\alpha]_D^{25}$ −69.0 (*c* 1.2, $CHCl_3$); IR (neat): 3449, 3060, 3028, 2925, 2854, 1727, 1646, 1602, 1492, 1383, 1258 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ 11.79 (s, 1H), 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 (125 MHz, Acetone-d_6): δ 173.5, 166.9, 166.0, 145.4, 141.2, 140.7, 134.0, 133.9, 130.0, 129.9, 129.6, 129.4, 129.2, 129.0, 108.6, 105.8, 101.5, 85.2, 80.2, 76.0, 75.0, 73.4, 56.8, 40.1, 36.5, 21.3 ppm; HRMS (ESI): calcd. for $C_{33}H_{36}O_7Na$ $[M + Na]^+$ 567.2358, found: 567.2340.

(3*S*,5*E*,8*S*,9*S*,11*E*)-8,9-Bis(benzyloxy)-16-hydroxy-14-methoxy-3-methyl-3,4,9,10-tetrahydro-1*H*-benzo[*c*][1]oxacyclotetradecine-1,7(8*H*)-dione (32): A solution of alcohol **31** (90 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) at 0 °C, was added Dess–Martin periodinane (110 mg, 0.26 mmol). The resulting reaction mixture was stirred at the same temperature for 3 h. After completion of the reaction (monitored by TLC), it was filtered through Celite bed and the filtrate was washed with saturated $NaHCO_3$ (2 x 5 mL). The organic layer was separated and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layer was dried over anhydrous Na_2SO_4, and the organic layer was removed under reduced pressure. Purification of the crude reaction mass by silica gel column chromatography (ethyl acetate/hexane = 1:19) afforded the corresponding keto **32** (83 mg, 90%) as a pale-yellow liquid. $[\alpha]_D^{25}$ −58.6 (*c* 0.5, $CHCl_3$); IR (neat): 3448, 2924, 2855, 1725, 1645, 1459, 1255 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.83 (s, 1H), 7.35-7.18 (m, 10H), 7.00 (m, 1H), 6.94 (d, *J* = 14.9 Hz, 1H), 6.59 (d, *J* = 15.9 Hz, 1H), 6.41 (s, 1H), 6.40 (s, 1H), 5.82 (m, 1H), 5.35 (m, 1H), 4.72-4.66 (m, 2H), 4.60-4.46 (m, 3H), 3.86-3.78 (s, 4H), 2.75-2.66 (m, 2H), 2.58-2.48 (m, 2H), 1.36 (d, *J* = 5.9 Hz, 3H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ 199.0, 170.9, 165.4, 164.0, 143.6, 142.9, 141.8, 138.1, 137.4, 133.3, 132.9, 130.8, 129.8, 128.3, 128.2, 127.8, 127.7, 127.7, 127.6, 108.6, 103.7, 100.1, 83.4, 80.3, 72.5, 71.7, 71.2, 55.4, 37.7, 35.3, 19.5 ppm; HRMS (ESI): calcd. for $C_{33}H_{34}O_7Na$ $[M + Na]^+$ 565.2202, found: 565.2190.

(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 (33): To a 10 mL round bottom flask charged with a magnetic stir bar was added (*S*)-CBS catalyst (66 mg, 0.24 mmol) THF (2 mL) under argon atmosphere. The reaction mixture was cooled to –40 °C and BH_3•Me_2S (0.12 mL, 0.24 mmol, 2M in THF) was added. To this reaction mixture, a solution of ketone **32** (65 mg, 0.12 mmol) dissolved in THF (2 mL) was added drop wise and stirred for 8 h at –40 °C. After completion of the reaction (monitored by TLC), the reaction was quenched with MeOH (1mL). The reaction mixture was diluted with saturated aqueous NH_4Cl (5mL) and extracted with ethyl acetate (3 x 5mL). The combined organic extracts were washed with brine (2 x 5mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude oil was purified by silica gel chromatography (ethyl acetate/hexane = 1:7) to furnish the desired alcohol **33** (49 mg, 82%) as a colorless liquid. $[\alpha]_D^{25}$ −61.3 (*c* 0.5, $CHCl_3$); IR (neat): 3449, 3060, 3028, 2925, 2854, 1727, 1646, 1602, 1492, 1383, 1258 cm^{-1}; ^1H NMR (500 MHz, Acetone-d_6): δ 11.91 (s, 1H), 7.49-7.12 (m, 11H), 6.46 (s, 1H), 6.38 (s, 1H), 6.08 (m, 1H), 5.95 (m, 1H), 5.80 (m, 1H), 5.29 (m, 1H), 4.97-4.43 (m, 4H), 4.35 (m, 1H), 3.95 (m, 1H), 3.85 (s, 3H), 3.65 (m, 1H), 2.65-2.46 (m, 4H), 1.46 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, Acetone-d_6): δ 173.5, 167.2, 166.0, 145.6, 141.5, 140.9, 134.0, 133.8, 133.4, 129.9, 129.6, 129.4, 129.0, 128.5, 108.6, 105.6, 101.5, 84.8, 83.9, 75.1, 74.3, 72.9, 56.9, 39.1, 35.9, 20.6 ppm; HRMS (ESI): calcd. for $C_{33}H_{38}O_7Na$ $[M + Na]^+$ 567.2358, found: 567.2340.

Zeaenol (1): To a stirred solution of **33** (45 mg, 0.08 mmol) in CH_2Cl_2 (5 mL) was added $TiCl_4$ (1.6 mL, 1.6 mmol, 1M in CH_2Cl_2) at 0 °C and the mixture was stirred for 30 min at 0 °C. After completion of the reaction (monitored by TLC), it was quenched with a saturated solution of $NaHCO_3$ (5 mL), extracted with CH_2Cl_2 (2 x 10 mL) and washed with brine (15 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 **1** (25 mg, 86%) as a white powder. $[\alpha]_D^{25}$ –89 (*c* 0.6, MeOH); IR (neat): 3424, 2926, 2854, 2738, 2489, 1607, 1637, 1385, 1254 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.83 (s, 1H), 7.12 (d, *J* = 14.9 Hz, 1H), 6.44 (d, *J* = 2.9 Hz, 1H), 6.39 (d, *J* = 2.9 Hz, 1H), 5.83 (ddd, *J* = 11.0, 4.0 Hz, 1H), 5.70 (dd, *J* =14.9, 7.9 Hz, 1H), 5.32 (m, 1H), 4.26 (t, *J* = 6.9 Hz, 1H), 3.98 (t, *J* = 6.9 Hz, 1H), 3.81 (s, 3H), 3.59 (d, *J* = 7.9 Hz, 1H), 2.60 (br s, 3 H), 2.55–2.25 (m, 4H), 1.46 (d, *J* = 6.9Hz, 3H) ppm; ^{13}C NMR

(125 MHz, $CDCl_3$): δ 171.2, 165.2, 164.0, 142.9, 133.6, 131.5, 129.2, 128.5, 107.6, 103.8, 100.0, 73.1, 71.9, 71.4, 55.4, 37.8, 35.9, 19.6 ppm; HRMS (ESI): calcd. for $C_{19}H_{24}O_7Na$ $[M + Na]^+$ 387.1417, found: 387.1426.

1,2,7,8-Tetrahydro-zeaenol (34): The compound **1** (13 mg, 0.035 mmol) was in MeOH (5 mL) and commercial Pd/C (10 mg, 10% w/w) was added in one portion. The resulting suspension was stirred under an atmosphere of H_2 for 24 h until complete disappearance of starting material occurred (monitored by TLC). The suspension was filtered through Celite pad and washed with ethyl acetate (10 mL). The combined filtrates were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (acetone/hexane = 1:1) to afford 2,7,8-tetrahydro-7-*epi*-Zeaenol (10 mg, 89%) as white power .as white power. $[\alpha]_D^{25}$ – 25 (*c* 0.4, $CHCl_3$); IR (neat): 3375, 2924, 2853, 1743, 1628, 1591, 1258 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 12.28 (s, 1H), 6.35 (d; *J* = 2.9 Hz, 1H), 6.26 (d, *J* = 1.9 Hz, 1H), 5.18 (m, 1H), 4.12 (d, *J* = 10.9 Hz, 1H), 3.93 (dd, *J* = 9.9, 3.9Hz, 1H), 3.80 (s, 3H), 3.63 (brs, 1H), 3.28 (td, *J* = 11.9 Hz, *J* = 3.9 Hz, 1H), 2.39 (m, 1H), 1.94-1.79 (m, 4H), 1.70-1.37 (m,6H), 1.37 (d, *J* =5.9 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ171.7, 166.6, 164.1, 147.1, 110.7, 104.4, 99.3, 75.7, 73.5, 69.9, 69.5, 55.3, 37.7, 34.7, 34.4, 31.9, 31.6, 28.7, 21.9, 21.5 ppm; HRMS(ESI): calcd. for $C_{19}H_{28}O_7Na$ $[M + Na]^+$ 391.1732, found: 391.1724.

(3*S*,5*E*,7*S*,8*S*,9*S*,11*E*)-8,9,16-Tris(benzyloxy)-14-methoxy-7-(methoxymethoxy)-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (35): To a suspension of NaH (60% in mineral oil , 9.2 mg, 0.23 mmol) in dry THF (2 mL), was added alcohol **29** (50 mg, 0.09 mmol) in THF (2 mL) at 0 °C. The suspension was stirred for 1 h at room temperature. The benzyl bromide (0.016mL, 0.14 mmol) was added slowly to the above reaction mixture at 0 °C. The reaction mixture was stirred at room temperature for additional 4 h and quenched with water at 0 °C. The reaction mixture was extracted with ethyl acetate (2 x 5 mL). The combined organic layer was washed with brine solution (10 mL), dried over anhydrous Na_2SO_4 and the solvent removed under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:25) to give **35** (54 mg, 89%) as a light-yellow liquid $[\alpha]_D^{25}$ −49.8 (*c* 0.8, $CHCl_3$); IR (neat): 2933, 2953, 1604, 1460, 1257, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.47-7.14 (m, 16H), 6.56 (d, *J* = 1.8 Hz, 1H), 6.39 (d, *J* = 1.8 Hz, 1H), 6.25 (m, 1H), 5.44 (m, 1H), 5.10 (m, 3H), 4.94-4.84 (m, 2H), 4.69-4.49 (m, 4H), 4.37 (m, 1H), 4.01 (m, 2H), 3.77 (s, 3H), 3.67-3.55 (m, 2H), 3.35 (s, 3H), 2.53-2.41 (m, 2H), 2.37-2.12 (m, 2H), 1.19 (d, *J* = 6.2 Hz, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.0, 161.0, 156.4, 139.1, 137.8, 137.5, 136.5, 132.5, 131.8, 128.9, 128.6, 128.4, 127.9, 127.8, 127.4, 126.9, 126.8, 116.9, 101.0, 98.4, 93.3, 83.9, 78.8, 77.6, 73.6, 71.3, 70.8, 70.4, 55.4, 55.1, 39.6, 31.6, 21.6 ppm; MS [ESI]: *m/z* $[M + Na]^+$ 701:

(3*S*,5*E*,7*S*,8*R*,9*S*,11*E*)-8,9,16-Tris(benzyloxy)-7-hydroxy-14-methoxy-3-methyl-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (36): To a solution of compound **35** (45 mg, 0.07 mmol) in THF (5 mL) was treated with 2N HCl (5 mL) and allowed to stirred for 15 h at room temperature. After completion of the reaction (monitored by TLC), ethyl acetate (5 mL) and H_2O (5 mL) were added. The layers were separated and the aqueous phase extracted with ethyl acetate (2 x 5mL). The combined organic portion was washed with saturated sodium bicarbonate solution (2 x 15 mL) followed by brine solution (15 mL), dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (ethyl acetate/ hexane = 1:8) to give **36 (**38mg, 91%),) `as a colorless liquid. $[\alpha]_D^{25}$ −56.5 (*c* 0.7, $CHCl_3$); IR (neat): 3452, 2926, 2855, 1728, 1642, 1573, 1456, 1383, 1257 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ7.43-7.21 (m, 16H), 6.46 (s, 1H), 6.41 (s, 1H), 6.08 (m, 1H), 5.63 (m, 1H), 5.42 (m, 1H), 5.24 (m, 1H), 5.12-5.04 (m, 2H), 4.76-4.60 (m, 4H), 4.24 (m, 1H), 3.78 (s, 3H), 3.73-3.65 (m, 2H), 2.65 (m,1H), 2.49 (m, 1H), 2.40-2.27 (m, 2H), 1.24 (d, *J* = 6.59, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$):167.4, 161.2, 156.8, 138.5, 137.8, 136.6, 128.6, 128.5, 128.4, 128.3, 127.8, 127.7, 127.5, 127.1, 116.6, 98.9, 76.4, 75.1, 71.4, 70.4, 55.4, 39.4, 21.1 ppm; HRMS (ESI): calcd. for $C_{40}H_{42}O_7Na$ $[M + Na]^+$ 657.2822, found: 657.2825

(3*S*,5*E*,7*S*,8*S*,9*S*,11*E*)-8,9,16-tris(benzyloxy)-14-methoxy-3-methyl-7-((*R*)-2,2,2-trifluoro-1-methoxy-1-phenylethoxy)-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (36a): To a stirred solution of **36** (15 mg, 0.023 mmol), MTPA (8 mg, 0.035 mmol) and DMAP (9 mg, 0.071 mmol) in CH_2Cl_2 (3 mL) was treated with DCC (24 mg, 0.118 mmol) and the reaction mixture was stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to furnish the desired esters **36a** (16.3 mg, 82%) as a colorless oils. ^1H NMR (500M Hz, $CDCl_3$): δ7.55-7.09 (m, 21H), 6.45 (d, *J* = 2.23, 1H), 6.38 (s, 1H), 6.13 (m, 1H), 5.53-5.32 (m, 2H), 5.09-4.96 (m, 4H), 4.68-4.58 (m, 2H), 4.43-4.33 (m, 2H), 3.77 (s, 3H), 3.68-3.61 (m, 2H), 3.52 (s, 3H), 2.53-2.43 (m, 2H), 2.22-2.15 (m, 2H), 1.17 (d, *J* = 6.86Hz, 3H) ppm.

(3*S*,5*E*,7*S*,8*S*,9*S*,11*E*)-8,9,16-Tris(benzyloxy)-14-methoxy-3-methyl-7-((*S*)-2,2,2-trifluoro-1-methoxy-1-phenylethoxy)-3,4,7,8,9,10-hexahydro-1*H*-benzo[*c*][1]oxacyclotetradecin-1-one (36b): To a stirred solution of **36** (15 mg, 0.023 mmol), MTPA (8 mg, 0.035 mmol) and DMAP (9 mg, 0.071 mmol) in CH_2Cl_2 (3 mL) was treated with DCC (24 mg, 0.118 mmol) and the reaction mixture was stirred for 12 h. After completion of the reaction (monitored by TLC), the reaction mixture was quenched with saturated aqueous $NaHCO_3$. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the residue was purified by silica gel column chromatography (ethyl acetate/hexane = 1:19) to furnish the desired esters **36b** (17.5 mg, 88%)as a colorless oils**.** ^1H NMR (500M Hz, $CDCl_3$): 7.55-6.99 (m, 21H), 6.46 (d, *J* = 2.28Hz, 1H), 6.38 (s, 1H), 6.14 (m, 1H), 5.55-5.43 (m, 2H), 5.08-4.93 (m, 4H), 4.66 (m, 1H), 4.48 (m, 1H), 4.35 (m, 1H), 4.22 (m, 1H), 3.77 (s, 3H), 3.58 (s, 1H), 3.54-3.45 (m, 4H), 2.46 (m, 1H), 2.33 (m, 1H), 2.27-2.11 (m, 2H), 1.16 (d, *J* = 5.72, 3H) ppm.

Biological evaluation **Materials and methods Cell Cultures, Maintenance and Antiproliferative Evaluation:** The cell lines, A549, HeLa, DU 145 and MDA MB 231 (lung, cervical, prostate and breast cancer) which were used in this study were procured from American Type Culture Collection (ATCC), United States. The synthesized test compounds were evaluated for their *invitro* antiproliferative activity in these six different human cancer cell lines. A protocol of 48 h continuous drug exposure was used, and a SRB cell proliferation assay was used to estimate cell viability or growth. All the cell lines were grown in Dulbecco's modified Eagle's medium (containing 10% FBS in a humidified atmosphere of 5% CO_2 at 37 °C). Cells were trypsinized when sub-confluent from T25 flasks/60 mm dishes and seeded in 96-well plates in 100 µL aliquots at plating densities depending on the doubling time of individual cell lines. The microtiter plates were incubated at 37 °C, 5% CO_2, 95% air, and 100% relative humidity for 24 h prior to addition of experimental drugs and were incubated for 48 hrs with different doses (0.01, 0.1, 1, 10, 100 µM) of prepared derivatives**.** After 48 hours incubation at 37 °C, cell monolayers were fixed by the addition of 10% (wt/vol) cold trichloroacetic acid and incubated at 4 °C for 1h and were then stained with 0.057% SRB dissolved in 1% acetic acid for 30 min at room temperature. Unbound SRB was washed with 1% acetic acid. The protein –bound dye was dissolved in 10 mM Tris base solution for OD determination at 510 nm using a microplate reader (Enspire, Perkin Elmer, USA). Using the seven absorbance measurements [time zero, (Tz), control growth, (C), and test growth in the presence of drug at the five concentration levels (Ti)], the percentage growth was calculated at each of the drug concentrations levels. Percentage growth inhibition was calculated as:

[(Ti-Tz)/(C-Tz)] x 100 for concentrations for which Ti>/=Tz

[(Ti-Tz)/Tz] x 100 for concentrations for which Ti<Tz.

Three dose response parameters were calculated for each experimental agent. Growth inhibition of 50 % (GI_{50}) was calculated from [(Ti-Tz)/(C-Tz)] x 100 = 50, which is the drug concentration resulting in a 50% reduction in the net protein increase (as measured by SRB staining) in control cells during the drug incubation. The drug concentration resulting in total growth inhibition (TGI) was calculated from Ti = Tz. The IC_{50} (concentration of drug resulting in a 50% reduction in the measured protein at the end of the drug treatment as compared to that at the beginning) indicating a net loss of cells following treatment was calculated from [(Ti-Tz)/Tz] x 100 = –50. Values were calculated for each of these three parameters if the level of activity is reached; however, if the effect is not reached or is exceeded, the value for that parameter was expressed as greater or less than the maximum or minimum concentration tested.[23]

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†Electronic Supplementary Information (ESI) available: [Scanned copies of ^1H, ^{13}C NMR and HPLC data]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data.

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