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Stereoselective total synthesis of (−)-cleistenolide

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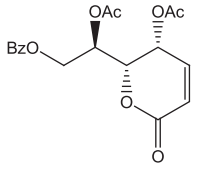
ABSTRACT

A stereoselective total synthesis of (−)-cleistenolide (**1**) derived from D-(−)-isoascorbic acid has been described. The new synthetic strategy involves highly diastereoselective reduction, one-pot protection of required benzoyl, acetyl groups, and the RCM reaction by using Grubbs catalyst are the key steps with considerable yields.

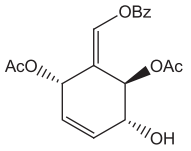
1. Introduction

The preamble of antibiotics greatly reduced the mortality due to infectious diseases.[1] However, the pathogens developing resistance to the antibiotics and host toxicity are some commonly encountered setbacks of recurring or continuous usage of these agents.[2] In view of these shortcomings, there is a constant need and demand for the identification and development of new antibacterial drugs. Natural products showing even marginal antibacterial activity are good source for new leads in drug discovery programs. As a general rule, the molecular configuration with surrounded functional groups offers the first insight of the pharmacophore entrenched in the compound for its biological activity. The biological activity of components usually depends on their functionality, configuration, and optical purity. Mainly in the antibacterial drug discovery, the lactone functionality is an important feature for antibacterial agents.[3] The tenacity needed to preserve the configuration and functionality of drugs from natural products call for estimable efforts and skills toward their synthesis in enantiomerically pure form.[4]

The natural products (−)-cleistenolide (**1**) and (−)-cleistodienol (**2**) are isolated from the medicinal plant *Cleistochlamys kirkii* found in Tanzania and Mozambique.[5] (−)-Cleistenolide is a six membered lactone having 2,3-dihydropyranone structure shows in vitro antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis* and antifungal activity against *Candida albicans*. The extracts of these plants are used in traditional medicine as a remedy for treatment of wound infections, rheumatism, and tuberculosis.[6] In this backdrop of biomedical significance, recently a couple of syntheses for (−)-cleistenolide are reported in the literature.[7]



(-)-Cleistenolide (**1**)



(-)-Cleistodienol (**2**)

Our research interest in the biologically active natural products and the structural features of α,β-unsaturated δ-lactone moiety with stereochemically defined tetrolsystem present in **1** gave impetus to the synthesis of (−)-cleistenolide (**1**). We have been working in the area of synthesis of biologically active natural products by using naturally available carbohydrates.[8] Out of several available carbohydrates, we found that D-(−)-isoascorbic acid is one of the best chiron source, which has been used for the total synthesis of many bioactive natural products.[9] Herein we are reporting a new approach, where D-(−)-isoascorbic acid is the starting material for the synthesis of (−)-cleistenolide (**1**).

In our retrosynthetic analysis of compound **1**, (Scheme 1) the intermediate acrylate ester (**11**) is derived from the compound (**9**) by sequel conversions of D-(−)-isoascorbic acid (**3**) including highly diastereoselective reduction and acrylation reactions.

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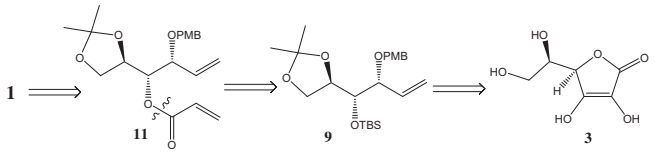
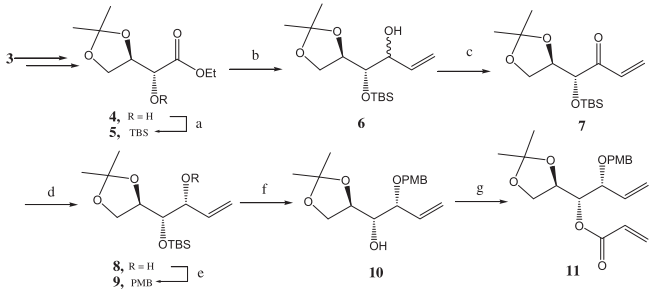


Scheme 1. Retrosynthetic analysis of cleistenolide (**1**).

2. Results and discussion

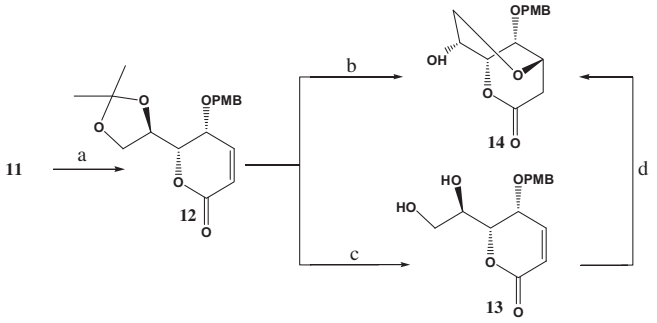
The synthesis of cleistenolide (**1**) started from commercially available sugar D-(−)-isoascorbic acid **3** (Scheme 2). Initially D-isoascorbic acid **3** was converted into α-hydroxy ester **4** using the literature procedure.[10] The hydroxyl group in compound **4** was protected with TBS group followed by the reduction with DIBAL-H to afford the aldehyde, which was subjected to Grignard reaction with vinyl magnesium bromide to afford the required allyl alcohol **6** in 73% yield. In order to obtain the compound **8** with 1,2-*syn* selectivity at chiral centers *C*3 and *C*4, the allylic alcohol **6** was first oxidized to allylic ketone **7** with IBX followed by selective reduction. This reduction step proved to be unexpectedly troublesome. A collection of reducing agents were screened, including (*R*)- and (*S*)-CBS·BH_3,[11] $NaBH_4/CeCl_3$,[12] LiBH4, Red-Al,[13] and L-Selectride. However, all these experiments resulted either in poor diastereoselectivity or no reaction. The reduction of **7** was next attempted with K-Selectride[14] under suitable reaction conditions (−78 °C, 6 h) to afford selectively diastereomeric alcohol **8** (>95:5) in isolated 91% yield. Stereochemistry of compound **8** was confirmed from the corresponding diacetonide compound using reported literature.[15]



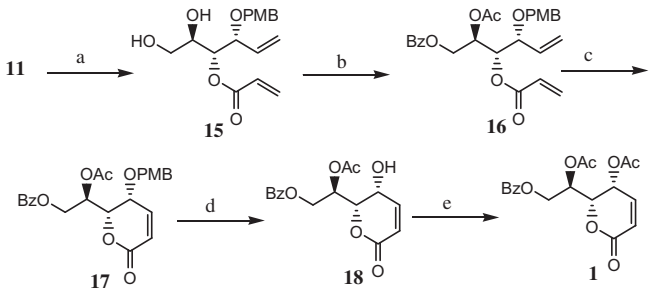
Scheme 2. Reagents and conditions: (a) TBDMSCl, imidazole, DCM, 2 h, rt, 94%; (b) (i) DIBAL-H, DCM, −78 °C, 30 min; (ii) Vinyl magnesium bromide, 0 °C to rt, 3 h, 73%; (c) IBX, DMSO, rt, 3 h; 96% (d) K-Selectride, −78 °C, 6 h, 91%; (e) PMB/Br, NaH, THF, rt, 1 h, 84%; (f) TBAF, THF, rt, 2 h, 96%; (f) Acryloyl chloride, Et_3N, DMAP, rt, 4 h, 86%.

The allylic alcohol in **8** was protected with PMB group and removal of TBS protection using TBAF selectively afforded corresponding alcohol **10** in 96% yield. The secondary alcohol in compound **10** was subjected to acrylation to obtain the intermediate diene **11** in considerable yield (86%), which was subjected to RCM reaction successfully using Grubbs second generation catalyst to obtain the compound **12** in 70% yield. The deprotection of isopropylidene group in cyclic compound **12**, was unsuccessful with different acidic catalysts like metal triflates, metal chlorides, CSA, *p*-TSA, aq HCl, AcOH etc., in protic solvent media, and afforded undesirable bicyclic product **14**. Finally, the acetonide group was removed using DOWEX-50 (H^+) resin in methanol to afford compound **13** (94% yield). Nevertheless, we have faced difficulty to incorporate the benzoyl group at primary alcohol in compound **13**. With the addition of simple base to compound **13**, it is undergoing to form predominantly bicyclic product **14** and unable to get the required product. The literature investigations are suggesting that, the oxa-Micheal addition mechanism may operate predominantly with the fully delocalization of electrons in unsaturated lactonic function of the compound **13**.[16–17]

With the strategic difficulty in Scheme 3, the isopropylidene group was deprotected in the compound **11** using DOWEX-50 (H^+)/MeOH early to the RCM reaction to prevent the oxa-Micheal addition to afford compound **15** in 95% yield. Here we applied one-pot synthetic strategy for benzoylation and acetylation by the sequential addition of pyridine and benzoyl chloride to compound **15** in dichloromethane followed by acetic anhydride to obtain the tri ester **16** in 85% yield. Now the tri ester was subjected to ring closing metathesis using Grubbs second generation catalyst to yield dihydropyranone derivative **17** in 69%. The *p*-methoxy benzyl group in **17** was removed with DDQ, which was further on acetylation delivered the natural product **1** in excellent yield as a colorless solid (Scheme 4). The physical and spectroscopic data of compound **1** were found to be identical with natural product (−) cleistenolide (**1**).[5]



Scheme 3. Reagents and conditions: (a) Grubbs second generation catalyst (5 mol %), DCM (0.02 mol/L), reflux, 12 h, 70%; (b) *p*-TSA, MeOH, rt, 2 h, 83%, (c) DOWEX-50 (H^+), MeOH, rt, 6 h, 94%; (d) Pyridine, DCM, rt, 30 min, 95%.



Scheme 4. Reagents and conditions: (a) DOWEX-50 (H^+), MeOH, rt, 6 h, 95%; (b) Pyridine, BzCl followed by Ac_2O, DCM, 0 °C to rt, 12 h, 85%; (c) Grubbs second generation catalyst, (5 mol %), DCM (0.01 mol/L), reflux, 12 h, 69%; (d) DDQ, Phosphate buffer solution: DCM (9:1), rt, 2 h, 88%; (e) Ac_2O, pyridine, DCM, rt, 2h, 89%.

3. Conclusions

In summary we are reporting a stereoselective total synthesis of (−)-cleistenolide (**1**) from D-isoascorbic acid **3** in 18% over all yield. Our synthetic route is very interesting with sequel reaction analyzations, including high diastereoselective reduction and RCM reactions.

4. Experimental section

4.1. General information

Commercial reagents were used without further purification, all solvents were purified by standard techniques and Infrared spectra were recorded on Perkin–Elmer 683 spectrometer. Optical rotations were obtained on Jasco Dip 360 digital polarimeter. NMR spectra were recorded in $CDCl_3$ solvent on Brucker 300 and Varian 500 NMR spectrometers. Chemical shifts (δ) are quoted in parts per

million and are referenced to tetramethylsilane (TMS) as an internal standard. Coupling constants (J) are quoted in Hertz. Column chromatographic separations were carried out on silica gel (60–120 mesh) and flash chromatographic separations were carried out using 230–400 mesh, silica gel. ESIMS was recorded on Agilent Technologies 1100 Series (Agilent Chemistation Software). HRMS was recorded on Agilent Technologies 6510 Q-TOF LC/MS.

4.2. Procedure: general experimental

*4.2.1. (R)-Ethyl2-(tert-butyldimethylsilyloxy)-2-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)acetate (**5**).* To a solution of **4** (5 g, 24.5 mmol) in dry DCM (50 mL) was added imidizole (2.4 g, 36.75 mmol) followed by TBSCl (3.95 g, 26.2 mmol). The reaction mixture was stirred for 5 h at room temperature After completion of the reaction as monitored by TLC, solvent was removed under reduced pressure and was purified over silica gel column chromatography (5% ethyl acetate in hexane) to furnish a pure compound **5** (7.32 g, 94%) as a colorless liquid. R_f=0.6 (EtOAc/hexane 1:9). $[\alpha]_D^{25}$ +24.5 (*c* 2.04, $CHCl_3$); IR (neat): ν 2933, 2859, 1750, 1473, 1371, 1256, 1155, 1074, 840, 779 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.26–4.12(4H, m), 3.98–3.96 (2H, d, J=5.28 Hz, OCH_2CH), 1.41 (3H, s), 1.33 (3H, s), 1.32–1.25 (3H, t, J=7.17 Hz, CH_3CH_2), 0.89 (9H, s, terbutyl), 0.08 (3H, s, MeSi), 0.07 (3H, s, MeSi); ^{13}C NMR (300 MHz, $CDCl_3$): δ 171.4, 109.5, 77.1, 72.6, 65.3, 60.9, 26.6, 25.6 (3C), 25.3, 18.1, 14.1, −5.0, −5.1; ESIMS: 341 $[M+Na]^+$; HRMS calculated for $C_{15}H_{30}O_5SiNa$ is 341.1760, found 341.1756.

*4.2.2. (1S,2S)-1-(tert-Butyldimethylsilyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (**6**).* To a cooled (−78 °C) solution of compound **5** (7.26 g, 22.7 mmol) in DCM (20 mL) was added DIBAL-H (22.7 mL of a 1 M soln in toluene, 22.7 mmol) and stirred for 4 h. After completion of the reaction as monitored by TLC, the reaction mixture was quenched with saturated aqueous sodium potassium tartarate solution (20 mL) and extracted into DCM, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to give crude aldehyde, which was subjected to next reaction without further purification. To a solution of crude aldehyde in dry THF (60 mL) at −78 °C was added vinyl magnesium bromide (34 mL of a 1 M soln in THF, 34 mmol) slowly over 20 min. The reaction mixture was stirred at the same temperature for 1 h and then slowly warmed to room temperature over 2 h. After completion of the reaction as monitored by TLC, the reaction was quenched with saturated NH_4Cl (20 mL) and extracted into EtOAc (3×15 mL). The combined organic extract was washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure which upon silica gel chromatography (5% ethyl acetate in hexane) furnished a pure compound **6** (5 g, 73%) as a yellow oil. R_f=0.4(EtOAc/hexane 1:9); IR (neat): ν 3473, 2955, 2858, 1727, 1254, 1073 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): 5.92–5.80 (1H, m, olefin), 5.35–5.28 (1H, td, J=15.67, 1.51 Hz, olefin), 5.22–5.18 (1H, td, J=10.57, 1.51 Hz, olefin), 4.24–4.20 (1H, m, CHOH), 4.06–4.00 (1H, m), 3.97–3.92 (1H, t, J=7.93 Hz), 3.89–3.85 (1H, dd, J=4.72, 3.39 Hz), 3.84–3.79 (1H, t, J=7.74 Hz), 2.47–2.38 (1H, br s, OH), 1.37 (3H, s), 1.30 (3H, s), 0.88 (9H, s, terbutyl), 0.10 (6H, s, Me_2Si); ^{13}C NMR (300 MHz, $CDCl_3$): 135.8, 116.8, 108.2, 75.8, 75.0, 72.3, 65.7, 26.5, 25.8 (3C), 25.5, 19.6, −4.3, −4.4; ESIMS: 325 $[M+Na]^+$; HRMS calculated for $C_{15}H_{30}O_4SiNa$ is 325.1811, found 325.1800.

*4.2.3. (R)-1-(tert-Butyldimethylsilyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-one (**7**).* To a solution of alcohol (4.9 g, 16.2 mmol) in dimethylsulfoxide (DMSO, 10 mL) was added 2-iodoxybenzoic acid (9 g, 32.4 mmol) at room temperature and stirred for 3 h at room temperature. After completion of the reaction, EtOAc (10 mL) was added to the reaction mixture. The suspension was filtered. To the filtrate cooled brine solution was added and extracted into EtOAc (3×15 mL). The combined EtOAc layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to give crude product, which was purified on silica gel chromatography (5% ethyl acetate in hexane) to furnish pure compound **7** as a pale yellow color oil (4.65 g, 96% yield). R_f=0.5 (EtOAc/hexane 1:9). $[\alpha]_D^{25}$ +15.5 (*c* 2.0, $CHCl_3$); IR (neat): ν 2931, 2894, 2858, 1702, 1613, 1256, 1077 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.83–6.74 (1H, m, olefin) 6.43–6.37 (1H, dd, J=1.5, 17.37 Hz, olefin), 5.80–5.76 (1H, dd, J=1.5, 10.5 Hz, olefin), 4.22–4.17 (2H, m), 4.0–3.9 (2H, m), 1.41 (3H, s), 1.31 (3H, s), 0.9 (9H, s, terbutyl), 0.08 (3H, s, MeSi), 0.02 (3H, s, MeSi); ^{13}C NMR (300 MHz, $CDCl_3$): δ 198.8, 131.4, 129.5, 109.7, 78.1, 76.9, 65.7, 26.4, 25.6 (3C), 25.2, 18.0, −4.8, −5.0; ESIMS: 323 $[M+Na]^+$; HRMS calculated for $C_{15}H_{28}O_4SiNa$ is 323.1649, found 323.1642.

*4.2.4. (1S,2R)-1-(tert-Butyldimethylsilyloxy)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (**8**).* To a cooled (−78 °C) solution of ketone **7** (4.6 g, 15.3 mmol) in toluene (40 mL) was added K-Selectride (30.4 mL, 1 M in THF, 30.4 mmol) and the reaction mixture was stirred for 6 h, allowing the temperature to warm slowly up to −40 °C. After completion of the reaction, the reaction was quenched with aq NH_4Cl (40 mL) and extracted into EtOAc (3×40 mL). The combined organic extract was dried over anhydrous $MgSO_4$ and concentrated under reduced pressure to give crude product, which was purified using silica gel chromatography (5% ethyl acetate in hexane) to afford allylic alcohol **8** (4.24 g, 91% yields) as a colorless oil. R_f=0.4 (EtOAc/hexane 1:9). $[\alpha]_D^{25}$ +37 (*c* 2.0, $CHCl_3$); IR (neat): ν 3473, 2955, 2858, 1627, 1254, 1073 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 6.01–5.87 (1H, m, olefin), 5.39–5.32 (1H, td, J=1.7, 17.1 Hz, olefin), 5.24–5.11 (1H, td, J=1.7, 10.7 Hz, olefin), 4.13–4.03 (2H, m), 3.99–3.94 (1H, m), 3.76–3.71 (2H, m, OCH_2), 2.59–2.53 (1H, br s, OH), 1.40 (3H, s), 1.31 (3H, s), 0.89 (9H, s, terbutyl), 0.11 (3H, s, MeSi), 0.08 (3H, s, MeSi); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.6, 115.72, 109.12, 76.2, 74.59, 73.82, 66.9, 26.82, 26.03 (3C), 25.47, 18.23, −3.84, −4.22; ESIMS: 325 $[M+Na]^+$; HRMS calculated for $C_{15}H_{30}O_4SiNa$ is 325.1811, found 325.1800.

*4.2.5. tert-Butyl((1S,2R)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxybenzyloxy)but-3-enyloxy)dimethylsilane (**9**).* To a cooled (0 °C) suspension of NaH (610 mg, 27.8 mmol) in dry THF (30 mL) was added a solution of alcohol **8** (4.2 g, 13.9 mmol) in dry THF (30 mL) followed by *p*-methoxy benzyl bromide (2.25 mL, 15.3 mmol) and reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction, the reaction was quenched with saturated NH_4Cl (50 mL) and extracted into EtOAc (3×50 mL). The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, and solvent concentrated under reduced pressure to give crude product, which was purified on silica gel column chromatography (5% ethyl acetate in hexane) to furnish pure PMB ether **9** (4.9 g, 84%) as a colorless liquid. R_f=0.6 (EtOAc/hexane 1:9). $[\alpha]_D^{25}$ +33(*c* 0.85, $CHCl_3$); IR (neat): ν 2954, 2930, 2857, 1512, 1250 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.29 (2H, d, J=8.1 Hz, ArH), 6.89–6.87 (2H, d, J=8.1 Hz, ArH), 5.97–5.90 (1H, m, olefin), 5.30–5.26 (1H, d, J=17.2 Hz, olefin), 5.14–5.12 (1H, d, J=9.9 Hz, olefin), 4.74–4.61 (2H, q, J=11.7, 50.8 Hz, OCH_2) 4.32–4.28 (1H, m, OCH), 4.22–4.21 (1H, m), 3.90–3.87 (2H, d, J=7.2 Hz), 3.8 (3H, s, OMe), 3.72–3.30 (1H, t, J=3.6 Hz), 1.43 (3H, s), 1.35 (3H, s), 0.91 (9H, s, terbutyl), 0.02 (6H, s, Me_2Si); ^{13}C NMR (300 MHz, $CDCl_3$): δ 159.0, 137.7, 130.7, 129.2 (2C), 115.0, 113.5 (2C), 81.5, 75.3, 73.7, 72.9, 65.0, 55.1, 26.3, 25.7 (3C), 25.0, 18.1, −4.8, −5.1; ESIMS: 445 $[M+Na]^+$; HRMS calculated for $C_{23}H_{38}O_5SiNa$ is 445.2381, found 445.2407.

*4.2.6. (1S,2R)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxy benzyloxy)but-3-en-1-ol (**10**).* To a cooled (0 °C) solution of **9** (4.8 g, 11.4 mmol) in THF (30 mL) was added tetrabutylammonium fluoride (17 mL of 1 M soln in THF, 17 mmol) and stirred for 4 h at room

temperature. After completion of the reaction as monitored by TLC, saturated $NaHCO_3$ was added and extracted into EtOAc (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine, dried (Na_2SO_4), concentrated, and the crude residue was purified by silica gel column chromatography (5% ethyl acetate in hexane) to afford **10** (3.37 g, 96%) as a colorless liquid. R_f=0.4 (EtOAc/hexane 1:9). $[\alpha]_D^{25}$ +33 (*c* 1.5, $CHCl_3$); IR (neat): *ν* 3471, 2986, 2934, 16,121, 1514, 1376, 1248 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.25–7.23(2H, d, *J*=8.37 Hz, ArH) 6.89–6.86 (2H, d, *J*=8.63 Hz, ArH), 6.04–5.93 (1H, m, olefin), 5.44–5.33 (1H, dd, *J*=1.5, 17.1 Hz, olefin), 5.27–5.23 (1H, dd, *J*=1.5, 12.0 Hz, olefin), 4.63–4.57 (2H, q, *J*=10.9, 13.5 Hz, OCH_2), 4.23–4.13 (2H, m), 4.05–3.97 (1H, m), 3.88–3.81 (1H, m), 3.80 (3H, s, OMe), 3.59–3.57 (1H, m), 2.70–2.63 (1H, br s, OH), 1.44 (3H, s), 1.34 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 159.4, 137.6, 129.8, 129.6 (2C), 116.1, 113.8 (2C), 109.0, 80.5, 75.8, 73.9, 72.0, 66.4, 55.2, 26.6, 25.2; ESIMS: 331 $[M+Na]^+$; HRMS calculated for $C_{17}H_{24}O_5Na$ is 331.1516, found 331.1516.

*4.2.7. (1S,2R)-1-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-2-(4-methoxy benzyloxy)but-3-enyl acrylate (**11**).* To a cooled (0 °C) solution of **10** (3.3 g, 10.7 mmol) in DCM (40 mL) was added Et_3N (2.23 mL, 21.4 mmol) followed by acryloyl chloride (1.7 mL, 21.4 mmol) and stirred for 4 h at room temperature. After completion of the reaction as monitored by TLC, water (40 mL) was added and extracted into DCM (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, and concentrated under reduced pressure to give crude product, which was purified over silica gel column chromatography (10% ethyl acetate in hexane) to afford **11** (3.33 g, 86%) as a colorless liquid. R_f=0.55 (EtOAc/hexane 2:8). $[\alpha]_D^{25}$ +66 (*c* 0.4, $CHCl_3$); IR (neat): *ν* 3441, 2988, 2936, 1727, 1513, 1250, 1186 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.27–7.23 (2H, d, *J*=8.3 Hz, ArH), 6.88–6.85 (2H, d, *J*=8.3 Hz, ArH), 6.48–6.40 (1H, dd, *J*=1.5, 17.3 Hz, olefin), 6.20–6.11 (1H, m, olefin), 5.95–5.84 (2H, m, olefin), 5.48–5.45 (1H, m, OCH), 5.36–5.24 (2H, m, olefin), 4.66 (2H, s, OCH_2), 4.19–4.08 (1H, m, OCH), 3.94–3.91 (2H, m), 3.82 (1H, m), 3.80 (3H, s, OMe), 1.41 (3H, s), 1.32 (3H, s); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 164.9, 159.2, 133.0, 131.3, 129.9, 129.6 (2C), 128.1, 118.6, 113.7 (2C), 108.6, 79.4, 75.8, 74.3, 74.2, 65.4, 55.2, 26.4, 25.2; ESIMS: 385 $[M+Na]^+$; HRMS calculated for $C_{20}H_{26}O_6Na$ is 385.1622, found 385.1620.

*4.2.8. (5R,6S)-6-((R)-2,2-Dimethyl-1,3-dioxolan-4-yl)-5-(4-methoxy benzyloxy)-5,6-dihydropyran-2-one (**12**).* To a degassed solution of acryl ester **11** (1 g, 2.76 mmol) in anhydrous DCM (100 mL) was added Grubbs second generation catalyst (117 mg, 5 mol %) and refluxed for 24 h. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to give crude product that was purified by column chromatography (15% ethyl acetate in hexane) to afford compound **12** (645 mg, 70%) as colorless liquid. R_f=0.3 (EtOAc/hexane 3:7). $[\alpha]_D^{25}$ +63 (*c* 0.48, $CHCl_3$); IR (neat): *ν* 2926, 1754, 1611, 1513, 1250, 1076 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.47–7.45 (1H, dd, *J*=1.5, 6.0 Hz, olefin), 7.22–7.19 (2H, d, *J*=9.0 Hz, ArH), 6.88–6.85 (2H, d, *J*=9.0 Hz, ArH), 6.14 (1H, m, olefin) 5.19 (1H, m, OCH), 4.65–4.60 (1H, d, *J*=11.3 Hz), 4.53–4.49 (1H, d, *J*=11.3 Hz), 4.19 (1H, m), 4.06 (1H, m), 3.82 (1H, m), 3.80 (3H, s, OMe), 3.56 (1H, m), 1.39 (3H, m), 1.34 (3H, m); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 173.3, 159.5, 153.3, 129.8 (2C), 129.6, 122.2, 113.8 (2C), 110.1, 84.2, 79.0, 75.3, 74.4, 66.9, 55.6, 26.6, 25.1; ESIMS: 357$[M+Na]^+$; HRMS calculated for $C_{18}H_{22}O_6Na$ is 357.1309, found 357.1301.

*4.2.9. (5R,6R)-6-((R)-1,2-Dihydroxyethyl)-5-(4-methoxy benzyloxy)-5,6-dihydropyran-2-one (**13**).* To a solution of **12** (250 mg, 0.74 mmol) in MeOH (20 mL) was added DOWEX-50 resin and the reaction mixture was allowed to stir for 6 h at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to give crude product that was purified over silica gel column chromatography (5% ethyl acetate in hexane). R_f=0.4 (EtOAc/hexane 6:4) to afford compound **13** (206 mg, 94%) as a white solid. $[\alpha]_D^{25}$ +128(*c* 0.45, $CHCl_3$); IR (KBr): *ν* 3451,1750, 1625, 1514, 1255, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.37 (1H, dd, *J*=1.8, 7.2 Hz, olefin), 7.20–7.18 (2H, d, *J*=8.2 Hz, ArH), 6.87–6.86 (2H, d, *J*=8.2 Hz, ArH), 6.14–6.12 (1H, m, olefin), 5.36 (1H, m), 4.53–4.45 (2H, q, *J*=11.8, 31.9 Hz, OCH_2) 3.86 (1H, m), 3.80 (3H, s, OMe), 3.77 (1H, d, *J*=3.6 Hz), 3.71–3.68(1H, m), 3.66–3.64 (1H, m), 2.06–1.56 (2H, br s, 2× OH); ^{13}C NMR (300 MHz, $CDCl_3$): 173.3, 159.4, 154.0, 129.9 (2C), 129.0, 122.1, 113.8 (2C), 83.6, 77.4, 74.0, 71.1, 63.1, 55.2; ESIMS: 317 $[M+Na]^+$; HRMS calculated for $C_{15}H_{18}O_6Na$ is 317.0996, found 317.1003.

*4.2.10. (1R,5S,8R,9R)-8-Hydroxy-9-(4-methoxybenzyloxy)-2,6-dioxa-bicyclo[3.3.1]nonan-3-one (**14**).* To a solution of **12** (250 mg, 0.74 mmol) in MeOH (20 mL) was added catalytic *p*-TSA and the reaction mixture was allowed to stir for 2 h at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to give crude product that was purified silica gel column chromatography (20% ethyl acetate in hexane) to afford compound **14** (183 mg, 83%) as a white solid. R_f=0.4 (EtOAc/hexane 2:3). $[\alpha]_D^{25}$ −3.5(*c* 0.5, $CHCl_3$); IR (KBr): *ν* 3465, 2927, 2859, 1737, 1237, 1169 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.28–7.23 (2H, d, *J*=9.0 Hz, ArH), 6.90–6.86 (2H, d, *J*=9.0 Hz, ArH), 4.87–4.86 (1H, d, *J*=4.5 Hz), 4.80–4.76 (1H, m), 4.63–4.49(2H, q, *J*=11.3, 27.9 Hz, OCH_2), 4.06–4.04 (1H, d, *J*=5.3 Hz), 3.98–3.93 (1H, m), 3.80 (3H, s, OMe), 3.77–3.76(1H, d, *J*=3.0 Hz), 3.65–3.59 (1H, m), 2.71 (2H, m, CH_2CO), 2.16–2.07 (1H, br s, OH); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 174.8, 159.5, 129.6 (2C), 128.6, 113.9 (2C), 87.8, 84.9, 82.7, 77.5, 72.4, 62.1, 55.2, 35.7; ESIMS: 317 $[M+Na]^+$; HRMS calculated for $C_{15}H_{18}O_6Na$ is 317.0996, found 317.1023.

*4.2.11. (2R,3R,4R)-1,2-Dihydroxy-4-(4-methoxybenzyloxy)hex-5-en-3-yl acrylate (**15**).* To a solution of **11** (1.5 g, 4.1 mmol) in MeOH (35 mL) was added DOWEX-50 resin and the reaction mixture was allowed to stir for 6 h at room temperature. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to give crude product that was purified by column chromatography (25% ethyl acetate in hexane) to afford compound **15** (1.26 g, 95%) as a colorless liquid. R_f=0.4 (EtOAc/hexane 1:1). $[\alpha]_D^{25}$ +58 (*c* 1.8, $CHCl_3$); IR (neat): *ν* 3430, 2929, 1722, 1613, 1514, 1407, 1249 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): *δ* 7.27–7.23 (2H, d, *J*=8.6 Hz, ArH), 6.88–6.85 (2H, d, *J*=8.6 Hz, ArH), 6.50–6.44 (1H, d, *J*=17.3 Hz, olefin), 6.24–6.14 (1H, m, olefin), 6.03–5.91 (1H, m, olefin), 5.90–5.86 (1H, d, *J*=10.3 Hz, olefin), 5.67–5.64 (1H, m, OCH), 5.42–5.36 (1H, d, *J*=17.1 Hz, olefin), 5.30–5.27 (1H, d, *J*=10.5 Hz, olefin), 4.67–4.52 (2H,q, *J*=10.9, 2.6 Hz, OCH_2), 3.79 (3H, s, OMe), 3.74–3.33 (4H, m), 3.16–2.56 (2H, br s, 2× OH); ^{13}C NMR (300 MHz, $CDCl_3$): *δ* 165.9, 159.3, 133.3, 131.8, 129.7 (2C), 127.9, 117.9, 113.7 (2C), 80.4, 74.4, 74.3, 70.4, 63.0, 55.1; ESIMS: 345 $[M+Na]^+$; HRMS calculated for $C_{17}H_{22}O_6Na$ is 345.1309, found 345.1325.

*4.2.12. (2R,3S,4R)-2-Acetoxy-3-(acryloyloxy)-4-(4-methoxybenzyloxy) hex-5-enyl benzoate (**16**).* To a cooled (0 °C) solution of diol **15** (1.1 g, 3.4 mmol) in DCM (15 mL) was added pyridine (1.10 mL, 13.6 mmol) followed by benzoyl chloride (0.4 mL, 3.4 mmol) and the reaction mixture stirred at the same temperature for 3 h. Acetic anhydride (0.3 mL, 3.4 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for additional 4 h. Water (10 mL) was added to the reaction mixture and extracted with DCM (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$, water, brine, dried (Na_2SO_4), concentrated, and the

residue was purified by column chromatography (7% ethyl acetate in hexane) to afford **16** (1.35 g, 85%) as a viscous liquid Compound. R_f=0.3 (EtOAc/hexane 1:9). Compound **16** $[\alpha]_D^{25}$ +27.3 (*c* 0.9, $CHCl_3$); IR (KBr): ν 2927, 1726, 1611, 1513, 1183, 1072 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.02–7.95 (2H, d, *J*=7.74 Hz, ArH), 7.61–7.52 (1H, t, *J*=7.36 Hz, ArH), 7.48–7.39 (2H, t, *J*=7.74 Hz, ArH), 7.28–7.22 (2H, d, *J*=8.68 Hz, ArH), 6.87–6.80 (2H, d, *J*=8.68 Hz, ArH), 6.50–6.41 (1H, m, olefin), 6.23–6.11 (1H, m, olefin), 6.05–5.83 (2H, m, olefin), 5.64–5.58 (1H, m, OCH), 5.47–5.45(1H, m, OCH) 541–5.25 (2H, m, olefin), 4.72–4.54 (3H, m), 4.48–4.39 (1H, m), 3.95–3.89 (1H, m), 3.77 (3H, s, OMe), 2.02 (3H, s, CH_3CO); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.8, 166.1, 165.1, 159.4, 133.1, 132.5, 131.5, 129.8 (2C), 129.7, 129.6 (2C), 129.2, 128.4 (2C), 128.0, 118.8, 113.8 (2C), 77.7, 74.1, 73.4, 70.2, 62.9, 55.2, 20.9; ESIMS: 491 $[M+Na]^+$; HRMS calculated for $C_{26}H_{28}O_8Na$ is 491.1676, found 491.1701.

*4.2.13. (R)-2-Acetoxy-2-((2S,3R)-3-(4-methoxybenzyloxy)-6-xo-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate (**17**).* To a degassed solution of diene ester **16** (500 mg, 1.06 mmol) in anhydrous DCM (100 mL) was added Grubbs second generation catalyst (44 mg, 5 mol %) and refluxed for 24 h. After completion of the reaction as monitored by TLC, the reaction mixture was filtered and the solvent was evaporated to give crude product that was purified by column chromatography (15% ethyl acetate in hexane) to afford **17** (320 mg, 69%) as a viscous liquid. R_f=0.4 (EtOAc/hexane 3:7). $[\alpha]_D^{25}$ +61.8(*c* 1.32, $CHCl_3$); IR (neat): ν 2924, 2853, 1751, 1724, 1514,1275 cm^{-1}; NMR (300 MHz, $CDCl_3$): δ 8.05–7.97 (2H, d, *J*=8.3 Hz, ArH), 7.61–7.56 (1H, t, *J*=7.5 Hz, ArH), 7.48–7.42 (2H, t, *J*=7.5 Hz, ArH), 7.42–7.39 (1H, dd, *J*=1.5, 6.0 Hz, olefin), 7.22–7.19 (2H, d, *J*=8.3 Hz, ArH), 6.85–6.82 (2H, d, *J*=8.3 Hz, ArH), 6.21–6.18 (1H, dd, *J*=2.2, 6.0 Hz, olefin), 5.26–5.20 (1H, m, OCH), 5.12–510 (1H, m, OCH), 4.79–4.74 (1H, dd, *J*=3.0, 12.0 Hz), 4.61–4.53 (2H, m, OCH_2), 4.47–4.41 (1H, dd, *J*=5.2, 12.8 Hz), 3.98–3.95 (1H, d d, *J*=3.7, 6.7 Hz, OCH), 3.76 (3H, s, OMe), 2.04 (3H,s, CH_3CO); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.8, 166.0, 164.6, 159.6, 152.3, 133.2, 130.0 (2C), 129.8, 129.5 (2C), 128.5 (2C), 124.9, 123.2, 113.9 (2C), 82.6, 75.4, 74.0, 71.3, 62.3, 55.2, 20.8; ESIMS: 463 $[M+Na]^+$; HRMS calculated for $C_{24}H_{24}O_8Na$ is 463.1363, found 463.1379.

*4.2.14. (R)-2-Acetoxy-2-((2S,3R)-3-hydroxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate (**18**).* To a solution of allyl ester (250 mg, 0.56 mmol) in CH_2Cl_2/phosphate buffer solution (9:1, 10 mL, pH 7.2) at ambient temperature was added DDQ (161 mg, 0.7 mmol). The reaction mixture was stirred for 1 h and the reaction mixture was diluted with CH_2Cl_2, filtered and the organic layer was washed with H_2O, dried over Na_2SO_4, and concentrated under reduced pressure. The crude residue was purified over silica gel column chromatography (18% ethyl acetate in hexane) to afford (160 mg, 88%) of **18** as a white solid. R_f=0.2 (EtOAc/hexane 3:7). $[\alpha]_D^{25}$ −29.5(*c* 0.45, $CHCl_3$); IR (KBr): 3427, 2924, 2854, 1724, 1277, 1229 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 8.05–8.01 (2H, d, *J*=8.0 Hz, ArH), 7.63–7.58 (1H, t, *J*=7.7 Hz, ArH), 7.49–7.47 (1H, d, *J*=2.37 Hz, olefin), 7.46–7.43 (2H, t, *J*=7.6 Hz, ArH), 6.24–6.21 (1H, dd, *J*=2.2, 6.0 Hz, olefin), 5.25–5.20 (1H, m, OCH), 5.25–5.15 (1H, m, OCH), 4.78–4.65 (2H, qd, *J*=3.7 Hz, 12.0 Hz, 16.6 Hz,), 4.08–4.02 (1H, td, *J*=3.02 Hz, OCH), 2.06 (3 H, s, CH_3CO), 2.03–1.56 (1H, br s, OH); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.8, 166.7, 164.3, 153.3, 133.4, 129.7 (2C), 128.5 (2C), 123.1, 82.2, 71.9, 68.9, 68.9, 62.5, 20.9; ESIMS: 343 $[M+Na]^+$; HRMS calculated for $C_{16}H_{16}O_7Na$ is 343.0788, found 343.0803.

*4.2.15. Cleistenolide (**1**).* To a cooled (0 °C) solution of alcohol **18** (100 mg, 0.31 mmol) in DCM (15 mL) was added pyridine (0.03 mL, 0.38 mmol) followed by acetic anhydride (0.03 mL, 0.31 mmol) to the reaction mixture and stirred at room temperature for 4 h. After completion of the reaction, water (10 mL) was added to the reaction mixture and extracted with DCM (3×15 mL). The combined organic layer was washed with saturated $NaHCO_3$, water, brine, dried (Na_2SO_4), concentrated, and the residue was purified over silica gel column chromatography (15% ethyl acetate in hexane) to afford **1** (100 mg, 90%) as a white solid. R_f=0.5 (EtOAc/hexane 3:7). Mp 132–134 °C. $[\alpha]_D^{25}$ −142 (*c* 0.4, $CHCl_3$); IR (KBr): ν 2963, 1725, 1452, 1372, 1224, 1099, 1070 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 8.02 (2H, d, *J*=7.7 Hz), 7.57 (1H, t, *J*=7.5 Hz), 7.45 (2H, t, *J*=7.6 Hz), 7.00 (1H, dd, *J*=9.6, 6.1 Hz), 6.29 (1H, d, *J*=9.7 Hz), 5.52 (1H, ddd, *J*=9.5, 4.0, 2.3 Hz), 5.42 (1H, dd, *J*=6.0, 2.5 Hz), 4.93 (1H, dd, *J*=12.5, 2.0 Hz), 4.80 (1H, dd, *J*=9.6, 2.5 Hz), 4.53 (1H, dd, *J*=12.5, 4.4 Hz), 2.09 (3H, s, CH_3CO), 2.04 (3H, s, CH_3CO); ^{13}C NMR (300 MHz, $CDCl_3$): δ 169.9, 169.5, 166.0, 161.1, 139.7, 133.3, 129.7 (2C), 129.6 (2C), 128.5, 125.4, 75.5, 67.7, 62.0, 59.7, 20.7, 20.5; ESIMS: 385 $[M+Na]^+$; HRMS calculated for $C_{18}H_{18}O_8Na$ is 385. 1002, found 385.0992.

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