Total Synthesis of (−)-Cleistenolide

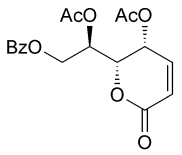
by **Dokuburra Chanti Babu**[a]), **Kankati Ashalatha**[a]), **Chitturi Bhujanga Rao**[a]), **Jon Paul Selvam Jondoss**[a]), and **Yenamandra Venkateswarlu***[a])

[a]) Natural Products Laboratory, Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad-500007, India (phone: +91-40-27193167; fax: +91-40-27160512; e-mail: luchem@iict.res.in)

An efficient and short total synthesis of (−)-cleistenolide (**1**) from D-mannitol with an overall yield of 23.6% is described. The chiron approach for the synthesis of (−)-cleistenolide involves a one-C-atom *Wittig* olefination, a selective allylic triethylsilyl protection, and a *Grubbs*-catalyzed ring-closure-metathesis (RCM) reaction as the key steps.

Introduction. – Antibacterial agents are gaining importance in drug therapy [1]. The introduction of antibiotics helps to drop the deaths rate from infectious diseases. For the treatment of infections caused by resistant bacteria, the antibacterial drugs such as teicoplanin, quinupristin/dalfopristin, and linezolid, *etc.*, are exhibiting side effects, and also their proficiency has been restricted by the development of bacterial-resistant mutants [2]. In view of tuning impediments, there is a necessity to identify and develop new antibacterial drugs. 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]. Hence, there is a need for worthy efforts and skills towards the synthesis of lactones in enantiomerically pure form [4].

(−)-Cleistenolide (**1**) and (−)-cleistodienol (**2**) are natural products isolated from the medicinal plant *Cleistochlamys kirkii* found in Tanzania and Mozambique [5]. (−)-Cleistenolide is a six-membered lactone with a 5,6-dihydro-2*H*-pyran-2-one structure, which showed *in vitro* antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis* and antifungal activity against *Candida albicans*. The extracts of this plant are used in traditional medicine as a remedy for treatment of wound infections, rheumatism, and tuberculosis [6]. In the recent past, a few syntheses of (−)-cleistenolide have been reported [7].



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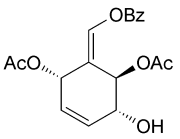


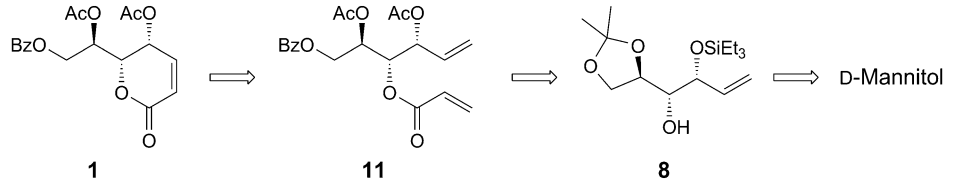
2

In continuation of our interest in the synthesis of biologically active natural products [8], we were interested in the synthesis of compound **1**, which contains an α,β-

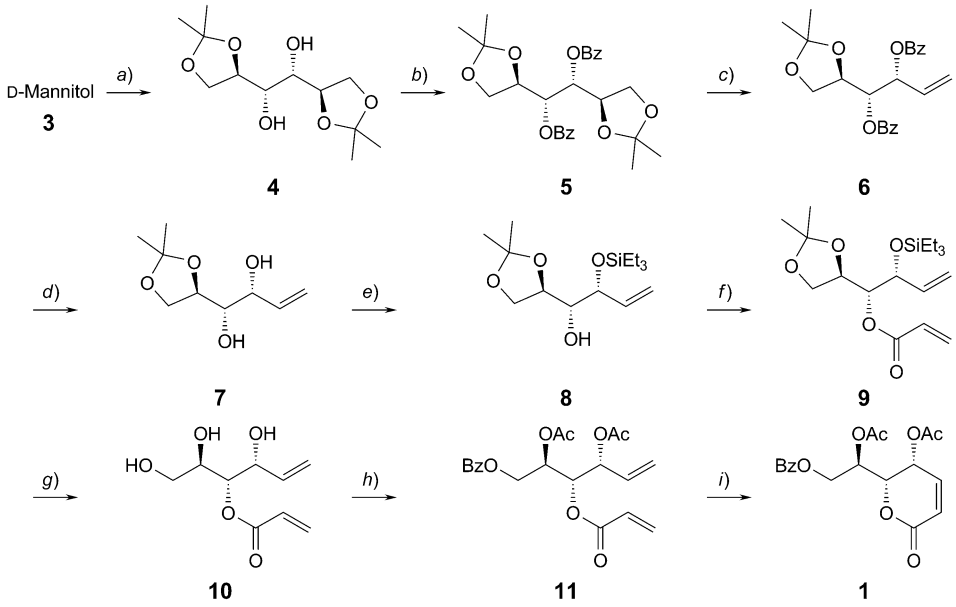
unsaturated δ-lactone moiety with a configurationally defined tetrol system. We started our synthesis from D-mannitol to furnish the natural product (−)-cleistenolide (**1**).

Results and Discussions. – The retrosynthetic analysis of compound **1** conceives that lactone **1** could be easily obtained from ester **11** by a ring-closing-metathesis (RCM) reaction via the mono-triethylsilyl-protected intermediate **8** (*Scheme 1*). The later can be easily derived from D-mannitol (**3**) *via* the procedure shown in *Scheme 2.*

Scheme 1. *Retrosynthetic Analysis of (−)-Cleistenolide* (**1**)



Scheme 2



a) $Me_2C(OMe)_2$, DMSO, TsOH (cat.), 6 h, r.t.; 79%. *b*) Et_3N, BzCl, CH_2Cl_2, 50°, 6 h; 91%. *c*) 1) H_5IO_6, Et_2O, r.t., 6 h, $NaHCO_3$. 2) ^{t}BuOK, $Ph_3PCH_3^+Br^-$, THF, −10°, 4 h; 71%. *d*) K_2CO_3, MeOH, r.t., 3 h; 91%. *e*) Et_3SiCl, 1*H*-imidazole, *N*,*N*-dimethylpyridin-4-amine (DMAP), CH_2Cl_2/DMF 1:1, −78°, 1 h; 90%. *f*) Acryloyl chloride, Et_3N, CH_2Cl_2, r.t., 4 h; 84%. *g*) *Dowex-50* (H^+), MeOH, r.t., 6 h; 94%. *h*) BzCl, pyridine, followed by Ac_2O, 0° to r.t., 7 h; 85%. *i*) *Grubbs*' second-generation catalyst (5 mol-%), CH_2Cl_2, reflux, 5 h; 85%.

Thus, D-mannitol (**3**) was treated with 2,2-dimethoxypropane ($Me_2C(OMe)_2$) in DMSO in the presence of *p*-toluenesulfonic acid (TsOH) to afford the corresponding 1,2:5,6-di-*O*-isopropylidene-protected diol **4** as a white solid [9] (*Scheme 2*). The latter

was further treated with benzoyl chloride (BzCl) in the presence of Et_3N in CH_2Cl_2 to afford 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-benzoyl-protected derivative **5** [10] in 91% yield. Compound **5** was treated with orthoperiodic acid (H_5IO_6) followed by $NaHCO_3$ in Et_2O at room temp. to yield the corresponding aldehyde [11] which was further converted into alkene **6** *via* a *Wittig* reaction. The two Bz protecting groups of **6** were removed by reaction with K_2CO_3/MeOH to afford diol **7** in 91% yield. The sterically less hindered allylic OH group in **7** was selectively protected as triethylsilyl ether by reacting **7** with Et_3SiCl and 1*H*-imidazole in CH_2Cl_2/DMF 1:1 at $-78°$ to obtain compound **8** as a colorless liquid in 90% yield [12]. The mono-triethylsilyl ether **8** was treated with acryloyl chloride in the presence of Et_3N to give the corresponding acrylate **9** in 84% yield. We tried to deprotect the isopropylidene and triethylsilyl ether group in a one-pot reaction with various reagents such as TsOH, camphorsulfonic acid (CSA), and other acids in MeOH, without success.

Finally, we achieved the deprotection of both groups by treatment with *Dowex-50* (H^+) resin in MeOH to afford the desired triol intermediate **10** in 94% yield. Compound **10** was treated with BzCl in pyridine followed by Ac_2O in a one-pot procedure to furnish diolefinic tetraester **11** in 85% yield. The latter was subjected to ring-closing metathesis (RCM) by using *Grubbs*' second-generation catalyst in CH_2Cl_2 to afford the natural product (−)-cleistenolide (**1**) in 85% yield as a colorless solid. The physical and spectroscopic data of the synthesized compound **1** were identical to those of the natural product [5].

Conclusion. – Among the reported five synthesis of (−)-cleistenolide (**1**), three used D-mannitol as starting material, and two other used D-arabinose and (−)-D-isoascorbic acid, respectively. In the present synthesis, we took advantage of all the stereogenic centers of D-mannitol. Thus the obtained diol **7** was selectively protected with Et_3SiCl, and the product was treated with acryloyl chloride to give acrylate **9**. In a one-pot procedure, the hydroxy derivative **10** was reacted sequentially with BzCl and Ac_2O to afford tetraester **11**, which on ring-closing-metathesis (RCM) reaction in the presence of *Grubbs*' second-generation catalyst afforded (−)-cleistenolide (**1**).

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Experimental Part

General. Solvents were dried over standard drying agents and freshly distilled prior to use. The reagents were purchased from *Aldrich* and *Acros* and were used without further purification unless otherwise stated. All moisture-sensitive reactions were carried out under N_2. Org. solns. were dried (Na_2SO_4) and concentrated *in vacuo* below 40°. Column chromatographic (CC): silica gel (SiO_2, 60–120 mesh; *Acme's*). Optical rotations: *HoribaSEPA-300* high-sensitive polarimeter; at 25°. IR Spectra: *Perkin-Elmer-IR-683* spectrophotometer with NaCl optics; $\tilde{\nu}$ in cm^{-1}. ^1H- (300 MHz) and ^{13}C-NMR (75 MHz) Spectra: *Bruker-Avance-300* instrument; in $CDCl_3$; δ in ppm rel. to Me_4Si as internal standard, *J* in Hz. MS: *Agilent Technologies 1100* series (Agilent Chemistation Software); in *m*/*z*.

1,2-Bis(2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diyl Dibenzoate (=*1,2:5,6-Bis*-O-*(1-methylethylidene)*-D-*mannitol Dibenzoate*; **5**) [10]. To a stirred soln. of diol **4** [9] (5 g, 19.08 mmol) and Et_3N (7.96 ml, 57.24 mmol) in dry CH_2Cl_2 (30 ml) was added BzCl (4.87 ml, 41.96 mmol) at 0° under N_2. After completion of the reaction, the mixture was diluted with H_2O (20 ml) and extracted with CH_2Cl_2 (3 ×

15 ml), the org. phase washed with brine (2 × 10 ml), dried (Na_2SO_4), and concentrated, and the crude residue purified by CC (AcOEt/hexane 1:9): **5** (8.1g, 91%). White solid. M.p. 82–85°. $[\alpha]_D^{25} = -113.9$ ($c = 3.4$, $CHCl_3$). IR (KBr): 3433, 3062, 2991, 2896, 1727, 1600, 1453, 1378, 1206, 1112, 1067. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.02 (*t*, *J* = 6.7, 4 H); 7.53 (*t*, *J* = 6.7, 2 H); 7.41 (*t*, *J* = 7.5, 4 H); 5.48 (*d*, *J* = 5.2, 1 H); 4.88 (*q*, *J* = 6.0, 1 H); 4.37 (*q*, *J* = 6.0, 2 H); 4.11 (*dd*, *J* = 5.2, 11.3, 1 H); 3.96 (*q*, *J* = 9.0, 2 H); 3.70 (*q*, *J* = 6.7, 1 H); 1.52 (*s*, 3 H); 1.44 (*s*, 3 H); 1.34 (*s*, 3 H); 1.31 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 165.5; 165.4; 133.12 (2 C); 129.8 (2 C); 129.6 (4 C); 128.3 (4 C); 108.9; 108.4; 74.5; 70.5; 69.8; 66.2; 66.1; 62.1; 26.9; 26.5; 25.4; 25.0. ESI-MS: 493 ($[M + Na]^+$).

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-ene-1,2-diyl Dibenzoate (*1,2-Dideoxy-5,6*-O-(*1-methylethylidene*)-D-arabino-*hex-1-enitol 3,4-Dibenzoate*; **6**). To a soln. of **5** (5 g, 10.6 mmol) in dry Et_2O (45 ml) was added H_5IO_6 (3.32 g, 14.56 mmol) at 0°, and the mixture was stirred for 6 h at r.t. The mixture was neutralized with $NaHCO_3$ (3.5 g), stirred for 30 min, and filtered through a *Celite* pad. The filtrate was evaporated to give the crude aldehyde, which was used as such for the next reaction without purification. To a cooled (−10°) soln. of Ph_3PCH_3Br (8.38 g, 21.2 mmol) in THF (30 ml) was added ^{t}BuOK (2.26 g, 20.1 mmol) portionwise, and the mixture was stirred for 2 h at r.t. To this mixture, a soln. of aldehyde in dry THF (20 ml) was added slowly at −10 min and then stirred at −10° for 2 h. After completion of the reaction TLC monitoring, the mixture was quenched by addition of sat. NH_4Cl soln. (20 ml) and extracted with AcOEt (3 × 15 ml). The combined extract was washed with brine, dried (Na_2SO_4) and concentrated and the crude residue purified by CC (AcOEt/hexane 5:95): **5** (2.94 g, 71%). Colorless solid. $[\alpha]_D^{25} = +35.3$ ($c = 1.5$, $CHCl_3$). IR (KBr): 2915, 2855, 1695, 1602, 1256, 1067, 710. ^{1}H-NMR (300 MHz, $CDCl_3$): 8.13 (*d*, *J* = 8.30, 4 H); 7.63 (*t*, *J* = 7.54, 2 H); 7.49 (*t*, *J* = 7.54, 4 H); 5.83–5.97 (*m*, 2 H); 5.61–5.66 (*m*, 1 H); 5.23–5.45 (*m*, 2 H); 4.39–4.47 (*m*, 1 H); 4.03–4.09 (*m*, 2 H); 1.34 (*s*, 3 H); 1.32 (*s*, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 165.64; 165.21; 138.17; 132.14 (2 C); 129.74 (2 C); 129.68 (4 C); 129.31 (4 C); 118.95; 109.61; 74.4; 73.49 (2 C); 65.74; 26.45; 25.21. ESI-MS: 419 ($[M + Na]^+$).

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)but-3-ene-1,2-diol (=*1,2-Dideoxy-5,6*-O-(*1-methylethylidene*)-D-arabino-*hex-1-enitol*; **7**) [13]. To a cooled (0°) soln. of **6** (2.9 g, 7.43 mmol) in MeOH (20 ml) was added K_2CO_3 (2.46 g, 17.8 mmol), and the mixture was stirred for 3 h at r.t. After completion of the reaction (TLC monitoring), the mixture was filtered and the solvent evaporated. The residue was diluted with H_2O (10 ml), the mixture extracted with AcOEt (3 × 15 ml), the combined extract washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 3:7): **7** (1.27 g, 91%). Colorless oil. $[\alpha]_D^{25} = +13.6$ ($c = 1.7$, $CHCl_3$). IR (neat): 3419, 2986, 2926, 1643, 1376, 1065. ^{1}H-NMR (300 MHz, $CDCl_3$): 5.88–6.01 (*m*, 1 H); 5.33–5.42 (*m*, 1 H); 5.22–5.30 (*m*, 1 H); 4.21–4.27 (*m*, 1 H); 3.93–4.16 (*m*, 3 H); 3.59 (*dd*, *J* = 3.39, 6.23, 1 H); 2.84 (br. *s*, 2 H); 1.43 (*s*, 3 H); 1.36 (*s*, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 137.29; 116.77; 109.12; 75.47; 73.78; 72.03; 66.04; 26.6; 25.19. ESI-MS: 211 ($[M + Na]^+$).

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-[(triethylsilyl)oxy]but-3-en-ol (=*1,2-Dideoxy-5,6*-O-*(1-methylethylidene)-3*-O-*(triethylsilyl)*-D-arabino-*hex-1-enitol*; **8**). To a cooled (−78°) soln. of **7** (1.1 g, 5.84 mmol), 1*H*-imidazole (0.45 g, 6.7 mmol), and DMAP (35mg, 0.29 mmol) in CH_2Cl_2/DMF 1:1 (20 ml) was added Et_3SiCl (1.03 ml, 6.4 mmol) dropwise over 5 min. The mixture was stirred for 1 h at −78°, warmed to r.t., then quenched by addition of sat. NH_4Cl soln., and diluted with AcOEt/hexane 1:1. The aq. phase was extracted with AcOEt/hexane 1:1 (3 × 10 ml), the combined extract washed with brine, dried (Na_2SO_4), and concentrated, and the residue purified by CC (AcOEt/hexane 1:9): **8** (1.58 g, 90%). Colorless liquid. $[\alpha]_D^{25} = +2.5$ ($c = 2.0$, $CHCl_3$). IR (neat): 3426, 2954, 2880, 1647, 1374, 1063. ^{1}H-NMR (500 MHz, $CDCl_3$): 5.98–5.84 (*m*, 1 H); 5.32–5.24 (*m*, 1 H); 5.20–5.14 (*m*, 1 H); 4.39–4.36 (*m*, 1 H); 4.17 (*t*, *J* = 7.84, 1 H); 3.99 (*q*, *J* = 6.86, 1 H); 3.93 (*t*, *J* = 7.84, 1 H); 3.34 (*t*, *J* = 7.84, 1 H); 1.82–1.63 (br. *s*, 1 H); 1.40 (*s*, 3 H); 1.34 (*s*, 3 H); 0.96 (*t*, *J* = 7.93, 9 H); 0.65 (*q*, *J* = 7.5, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.4; 115.7; 109.06; 75.5; 75.27; 72.68; 67.28; 26.77; 25.32; 6.72 (3 C); 4.88 (3 C). ESI-MS: 325 ($[M + Na]^+$).

1-(2,2-Dimethyl-1,3-dioxolan-4-yl)-2-[(triethylsilyl)oxy]but-3-en-1-yl Prop-2-enoate (=*1,2-Diheoxy-5,6-(1-methylethylidene)-3*-O-*(triethylsilyl)*-D-arabino-*hex-1-enitol 4-(Prop-2-enoate)*; **9**). To a cooled (0°) soln. of **8** (1.25 g, 4.1 mmol) in CH_2Cl_2 (20 ml) was added Et_3N (0.25 ml, 6.14 mmol) followed by acryloyl chloride (0.67 ml, 8.2 mmol), and the mixture was stirred for 4 h at r.t. After completion of the reaction (TLC monitoring), H_2O (15 ml) was added and the mixture extracted with CH_2Cl_2 (3 × 15 ml).

The combined org. layer was washed with sat. $NaHCO_3$, soln. and brine, dried (Na_2SO_4), and concentrated and the residue purified by CC (AcOEt/hexane 8:92): **9** (1.23 g, 84%). Colorless liquid. $[\alpha]_D^{25} = +30.8$ ($c = 2.35$, $CHCl_3$). IR (neat): 2955, 2880, 1732, 1635, 1460, 1406, 1259, 1184, 1063. ^{1}H-NMR (300 MHz, $CDCl_3$): 6.47–6.41 (*m*, 1 H); 6.19–6.07 (*m*, 2 H); 5.87–5.69 (*m*, 2 H); 5.31–5.25 (*m*, 1 H); 5.18–5.13 (*m*, 2 H); 4.37–4.28 (*m*, 1 H); 3.99–3.82 (*m*, 2 H); 1.32 (*s*, 6 H) 0.94 (*t*, $J = 7.93$, 9 H); 0.59 (*q*, $J = 7.5$, 6 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 165.28; 136.89; 131.67; 128.15; 116.52; 108.46; 75.44; 73.95; 72.32; 65.47; 26.31; 25.26; 6.69 (3 C); 4.73 (3 C). ESI-MS: 379 ($[M + Na]^+$).

(*1*S,*2*R)-*1-[(1*R*)-1,2-Dihydroxyethyl]-2-hydroxybut-3-en-1-yl Prop-2-enoate (=1,2-Dideoxy*-D-arabino-*hex-1-enitol 4-(Prop-2-enoate)*; **10**). To a soln. of **9** (1.2 g, 3.37 mmol) in MeOH (20 ml) was added *Dowex-50* (H^+) resin (100 mg), and the mixture was stirred for 6 h at r.t. After completion of the reaction (TLC monitoring), the mixture was filtered, the filtrate concentrated, and the residue purified by CC (AcOEt/hexane 7:3): **10** (0.64 g, 94%). Viscous liquid. $[\alpha]_D^{25} = +9.7$ ($c = 0.65$, $CHCl_3$). IR (neat): 3448, 2956, 2884, 1735, 1630, 1461. ^{1}H-NMR (500 MHz, $CDCl_3$): 6.51 (*d*, $J = 17.3$, 1 H); 6.23–6.09 (*m*, 1 H); 6.06–5.87 (*m*, 2 H); 5.41 (*d*, $J = 17.1$, 1 H); 5.29 (*d*, $J = 10.5$, 1 H); 4.48–4.35 (*m*, 3 H); 4.02–3.97 (*m*, 1 H); 3.56–3.54 (*m*, 1 H); 3.32–3.06 (br. *s*, 1 H); 3.02–2.77 (br. *s*, 1 H); 2.03–1.75 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$, 75 MHz): 166.9; 137.2; 131.9; 127.7; 117.1; 73.0; 71.8; 70.7; 66.1. ESI-MS: 225 ($[M + Na]^+$).

*(1*S*,2*R*)-2-(Acetyloxy)-1-[(1*R*)-1-(acetyloxy)-2-(benzyloxy)ethyl]but-3-en-1-yl Prop-2-enoate (=1,2-Dideoxy*-D-arabino-*hex-1-enitol 3,5-Diacetetate 6-Benzoate A-(Prop-2-enoate)* **11**). To a cooled (0°) soln. of **10** (0.6 g, 2.9 mmol) in CH_2Cl_2 (15 ml) was added pyridine (1.43 ml, 17.4 mmol) followed by BzCl (0.36 ml, 3.04 mmol), and the mixture stirred at 0° for 3 h. Then Ac_2O (0.65 ml, 7 mmol) was added and stirred at r.t. for additional 4 h. After completion of the reaction, the mixture was diluted with H_2O (10 ml) and extracted with CH_2Cl_2 (3 × 15 ml). The combined org. layer was washed with sat. $NaHCO_3$ soln., H_2O, and brine, dried (Na_2SO_4), and concentrated and the residue purified by CC (AcOEt/hexane 1:9); **11** (0.98 g, 85%). Viscous liquid. $[\alpha]_D^{25} = +25.6$ ($c = 0.55$, $CHCl_3$). IR (neat):2963, 1725, 1452, 1372, 1224, 1099, 1070. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.02 (*dd*, $J = 8.3$, 1.51, 2 H); 7.57 (*t*, $J = 7.55$, 1 H); 7.45 (*t*, $J = 7.55$, 2 H); 6.52–6.40 (*m*, 1 H); 6.22–6.09 (*m*, 1 H); 5.95–5.87 (*m*, 1 H); 5.84–5.72 (*m*, 1 H); 5.70–5.59 (*m*, 1 H); 5.57–5.48 (*m*, 1 H); 5.38–5.24 (*m*, 2 H); 5.16–5.10 (*m*, 1 H); 4.69–4.61 (*m*, 1 H); 4.38–4.27 (*m*, 1 H); 2.10 (*s*, 3 H); 2.06 (*s*, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 170.3; 169.75; 167.37; 166.47; 133.21; 132.51; 131.93; 131.52; 129.68 (2 C); 128.40 (2 C); 127.24; 119.16; 71.76; 70.69; 68.68; 62.25; 20.77 (2 C). ESI-MS: 413 ($[M + Na]^+$).

(−)-Cleistenolide (*=2,3-Dideoxy*-D-arabino-*hept-2-enoic Acid δ-Lactone 4,6-Diacetate 7-Benzoate;* **1**). To a degassed soln. of **11** (100 mg, 0.25 mmol) in anh. CH_2Cl_2 (100 ml) was added *Grubbs*' second-generation catalyst (10 mg, 0.012 mmol), and the mixture was refluxed for 5 h. After completion of the reaction (TLC monitoring), the mixture was filtered, the filtrate concentrated, and the residue purified by CC (AcOEt/hexane 3:7): **1** (79 mg, 85%). Colorless solid. M.p. 132–134°. $[\alpha]_D^{25} = -142$ ($c = 0.4$, $CHCl_3$). IR (KBr): 2963, 1725, 1452, 1372, 1224, 1099, 1070. ^{1}H-NMR (500 MHz, $CDCl_3$): 8.02 (*d*, $J = 7.7$, 2 H); 7.57 (*t*, $J = 7.5$, 1 H); 7.45 (*t*, $J = 7.6$, 2 H); 7.00 (*dd*, $J = 9.6$, 6.1, 1 H); 6.29 (*d*, $J = 9.7$, 1 H); 5.52 (*ddd*, $J = 9.5$, 4.0, 2.3, 1 H); 5.42 (*dd*, $J = 6.0$, 2.5, 1 H); 4.93 (*dd*, $J = 12.5$, 2.0, 1 H); 4.80 (*dd*, $J = 9.6$, 2.5,1 H); 4.53 (*dd*, $J = 12.5$, 4.4, 1 H); 2.09 (*s*, MeC=O); 2.04 (*s*, MeC=O). ^{13}C-NMR (75 MHz, $CDCl_3$): 169.9; 169.5; 166.0; 161.1; 139.7; 133.3; 129.7 (2 C); 129.6; 128.5 (2 C); 125.4; 75.5; 67.7; 62.0; 59.7; 20.7; 20.5. ESI-MS: 385 ($[M + Na]^+$). HR-MS: 385.0992 ($C_{18}H_{18}NaO_8^+$; calc. 385. 1002).

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