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A simple and efficient stereoselective synthesis of (−)-cleistenolide

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ABSTRACT

A simple and straightforward stereoselective synthesis of α,β-unsaturated δ-lactone, (−)-cleistenolide has been accomplished in 10 steps in an overall yield of 19%, starting from inexpensive and commercially available starting materials, respectively. This linear synthesis utilizes Sharpless asymmetric dihydroxylation, sulfur ylide mediated epoxide opening followed by ring-closing metathesis (RCM) for the formation of six-membered lactone ring as the key step sequence.

Natural products possessing α,β-unsaturated δ-lactone motif, has long been a privileged scaffold in drug discovery because of their diverse array of biological activities including their antifungal and antitumour properties.[1] α,β-Unsaturated δ-lactone unit is presumed to be an active pharmacophore responsible for biological activities as a result of its ability to act as a Michael acceptor.[2] Among these lactones, 5-hydroxy-α,β-unsaturated δ-lactones have attracted considerable attention due to their broad range of biological activities. Representative examples of this class of molecules are cleistenolide (**1**), pectinolide A (**2**), phomopsolide D (**3**), and acetylphomolactone (**4**) (Fig. 1). Cleistenolide (**1**), perhaps is the best example of these interesting compounds that have been isolated from the medicinal plant *Cleistochlamys kirkii* oliver,[3] that belongs to the family of annonaceae species with its origin from Tanzania and Mozambique. Cleistenolide (**1**) exhibits in vitro antibacterial activity against *Staphylococcus aureus*, *Bacillus anthracis* and antifungal activity against *Candida albicans*. Moreover, the extracts of this plant have been utilized for the treatment of wound infections, rheumatism, and tuberculosis.[4]

Owing to this combination of interesting structural features and potential biological activities of cleistenolide (**1**), synthesis of this compound has attracted much attention among organic chemists. Consequently, several syntheses have appeared in the literature. To date, only five total syntheses have been reported.[5] The first synthesis was reported by Schmidt et al.,[5a] using the mannitol derived (*R*,*R*)-1,5-hexadiene-3,4-diol as a starting material and other syntheses were achieved using D-arabinose,[5b] D-mannitol,[5c,d] and (−)-isoascorbic acid[5e] as starting materials. Despite the availability of many synthetic methods for this class of compounds, there still exists a need to develop procedures more efficient than those currently in existence. In continuation of our ongoing studies on the synthesis of bioactive natural products,[6] we have focused on the synthesis of (−)-cleistenolide because of its potential biological activities. Herein, we report short and straightforward stereoselective synthesis of (−)-cleistenolide starting from D-mannitol derived ester (*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl) with an overall yield of 19%. The synthesis involved the Sharpless asymmetric dihydroxylation, sulfur ylide mediated epoxide ring opening and Grubbs ring-closing metathesis as the key reaction sequence.

Our retrosynthetic analysis of the target compound (−)-cleistenolide is outlined in Scheme 1. As indicated, the cyclic frame work of **1** could be constructed by ring-closing metathesis (RCM) followed by PCC oxidation. The requisite diene **5**, in turn, could be accessed from the key intermediate **6** through allylation

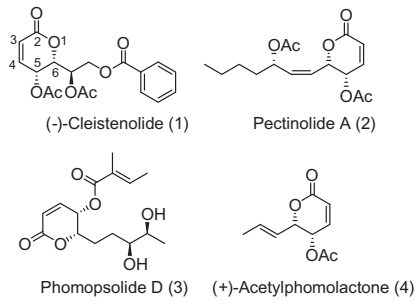

Figure 1. Reperesentative structures of some 5-substituted α,β-unsaturated δ-lactones.

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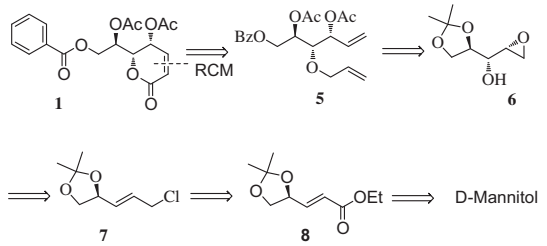
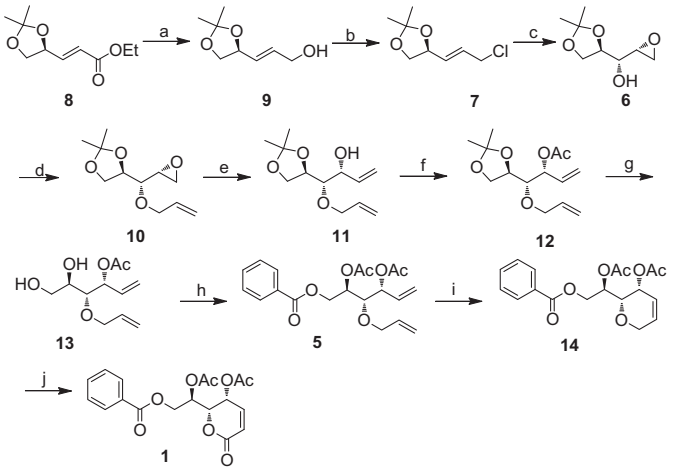


Scheme 1. Retrosynthetic analysis of **1**.



Scheme 2. Reagents and conditions: (a) DIBAL-H, CH_2Cl_2, 0 °C, 3 h, 91%; (b) PPh_3, CCl_4, $NaHCO_3$, reflux, 6 h, 75%; (c) (i) AD-mix-β, $CH_3SO_2NH_2$, $NaHCO_3$, *t*BuOH/H_2O, 0 °C, 24 h; (ii) NaOH, THF, 2 h, 0 °C–rt, 79% (over two steps); (d) allyl bromide, NaH, THF, 0 °C–rt, 3 h, 95%; (e) $(CH3)_3S^+I^-$, *n*-BuLi, −20 °C, 2 h, 94%; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C–rt, 1 h, 95%; (g) 60% aq AcOH, 0 °C–rt, 12 h, 90%; (h) (i) Py, BzCl, CH_2Cl_2, 0 °C–rt, 4 h; (ii) Ac_2O, 0 °C–rt, 4 h, 71% (over two steps); (i) Grubbs-II, CH_2Cl_2, reflux, 30 min, 90%; (j) PCC, Py, CH_2Cl_2, reflux, 8 h, 72%.

followed by sulfur ylide mediated epoxide ring opening. The key intermediate **6** could be obtained from Sharpless dihydroxylation of **7**, which was derived from D-mannitol in a few steps. This strategy, as a whole, relies on chiral starting material, D-mannitol and its derivative **6** as the key reaction intermediate. The key step was the highly stereospecific Sharpless dihydroxylation of mannitol derived ester **8** (Scheme 1). Although, our synthetic strategy also utilized D-mannitol as a starting material, we have successfully implemented a strategy that minimizes protecting group manipulation in a unique fashion, a common and unavoidable practice in (−)-cleistenolide synthesis.

As shown in Scheme 2, the synthesis of cleistenolide was started from enantiomerically pure (*S*,*E*)-ethyl 3-(2,2-dimethyl-1,3-dioxolan-4-yl)acrylate **8**, which was prepared from commercially available D-mannitol using the literature procedure.[7] The ester functionality in compound **8** was reduced to alcohol using DIBAL-H to furnish the corresponding allylic alcohol **9** in an excellent yield (91%). The stereochemistry of the double bond in **9** was confirmed as *E* by the large coupling constant (J = 15 Hz) observed from the ^{1}H NMR spectrum. Next, we have investigated the Sharpless asymmetric dihydroxylation[8] to install the two stereogenic centers in **1**. It is well known that allylic chlorides are excellent substrates for Sharpless asymmetric dihydroxylation.[9]

With this view, hydroxyl functionality in **9** was subjected to the Appel reaction conditions (triphenyl phosphine, CCl_4, reflux)[10] to afford its corresponding allylic chloride **7**. Subsequently, this allyl chloride **7** was subjected to Sharpless asymmetric dihydroxylation using AD-mix-β to give intermediate chloro-diol, which, without further purification, was treated with powdered NaOH in dry THF to give epoxide in a 79% yield as the key intermediate (over two steps) with 95% ee.[9]

The hydroxyl group in the key intermediate **6** was allylated using NaH and allyl bromide in THF to afford **10** in a 95% yield. With the allylated epoxide **10** in hand, we then shifted our focus to the regioselective ring opening of epoxide with dimethylsulfonium methylide (Me_3SI, *n*-BuLi) to afford allylic alcohol **11** in a 94% yield,[11] which was then acetylated with acetic anhydride in the presence of triethylamine and a catalytic amount of DMAP furnished the corresponding ester **12**. Subsequent acetonide deprotection with 60% aq AcOH afforded diol **13** in a 75% yield. Benzoylation of primary alcohol in **13** was with benzoyl chloride in the presence of pyridine in CH_2Cl_2 that gave the mono-benzoate which was, without further purification, acetylated by the addition of acetic anhydride to yield the triester **5** in an 80% yield. As mentioned in our retrosynthetic analysis, next stage of our plan involved the construction of six-membered δ-lactone ring by ring-closing metathesis. This may be considered as the most critical step in our synthetic scheme because the preparation of medium-sized rings by RCM may be difficult in some instances (especially from acyclic precursors) owing to entropic factors and transannular repulsions that develop as the ring is formed. Gratifyingly, and in spite of these potential problems, in our case treatment of **5** with Grubb's second generation catalyst (5 mol %) in dry DCM under reflux conditions yielded **14** in a 90% yield. Finally, the allylic methylene group in **14** was oxidized with PCC and pyridine in dry DCM that furnished the target compound, (−)-cleistenolide (**1**) in a 72% yield (Scheme 2).[12] The spectral data[13] (^{1}H NMR, ^{13}C NMR, and Mass data) derived from each of the intermediate compounds were in full accordance with those of the assigned structures. Furthermore, chirooptical data, spectroscopic, and physical data of compound **1** were identical in all respects to the data reported in the literature.[3,5a,b]

In conclusion, the stereoselective total synthesis of (−)-cleistenolide has been achieved by employing Sharpless asymmetric dihydroxylation, sulfurylide mediated epoxide opening and ring closing metathesis reactions as the key reaction sequence. On the basis of the route described herein, further work toward preparation of the library of analogues for biological analysis is in progress at our laboratory.

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13. Spectral data:
(2E,4S)-4,5-(O-Isopropylidene)-4,5-dihydroxyprop-2-en-1-ol (**10**): $[\alpha]_D^{25}$ +30.5 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 3414, 2988, 1721, 1689, 1377, 1216, 1157, 1061, 976 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.35 (s, 3H), 1.39 (s, 3H), 3.54 (t, *J* = 7.9, 15.8 Hz, 1H), 4.04 (br t, *J* = 7.9, 13.8 Hz, 1H), 4.13 (d, *J* = 4 Hz, 2H), 4.48 (dd, *J* = 6.9, 13.8 Hz, 1H), 5.67 (dd, *J* = 6.9, 14.8 Hz, 1H) 5.91 (dt, *J* = 4.94, 14.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7, 26.5, 62.3, 69.2, 76.4, 109.2, 128.1; ESIMS *m/z* 181 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_8H_{14}O_3Na$: 181.14352, found: 181.14375.
(S,E)-4-(3-Chloroprop-1-enyl)-2,2-dimethyl-1,3-dioxolane (**7**): $[\alpha]_D^{25}$ +20 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 2924, 2857, 1725, 1448, 1101, 972 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.36 (3H, s), 1.40 (3H, s), 3.57 (t, *J* = 7.9, 15.8 Hz, 1H), 4.02–4.05 (m, 2H), 4.08 (br t, *J* = 7.9, 14.8, 1H), 4.49 (dd, *J* = 6.9, 13.8 Hz, 1H), 5.76 (dd, *J* = 6.9, 14.8 Hz, 1H) 5.91 (dt, *J* = 4.94, 14.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.7, 26.6, 43.8, 69.1, 75.8, 109.5, 129.3, 132; ESIMS *m/z* 177 $(M+H)^+$: ESI-HRMS: *m/z* calcd for $C_8H_{13}ClO_2$: 177.85246, found: 177.92344.
(S)-((S)-2,2-Dimethyl-1,3-dioxolan-4-yl)((R)-oxiran-2-yl)methanol (**6**): $[\alpha]_D^{25}$ −20 (*c* 0.75, $CHCl_3$); IR (KBr) ν_{max} 3440, 2990, 1640, 1377, 1256, 1216, 1155, 1066, 849 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.34 (s, 3H), 1.40 (s, 3H), 2.75–2.77 (m, 1H), 2.80–2.82 (m, 1H), 3.17–3.19 (m, 1H), 3.44–3.49 (m, 1H), 3.96 (dd, *J* = 4.9, 7.9, 1H), 4.02 (dd, *J* = 5.9, 12.8, 1H), 4.08 (dd, *J* = 5.9, 7.9, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.02, 26.5, 44.5, 52.4, 66.5, 71.2, 76.4, 109.5; ESIMS *m/z* 197 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_8H_{14}O_4Na$: 197.11025, found: 197.11062.
(S)-4-((S)-Allyloxy((R)-oxiran-2-yl)methyl)-2,2-dimethyl-1,3-dioxolane (**11**): $[\alpha]_D^{25}$ −4.5 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 2926, 2856, 1459, 1375, 1257, 1075, 920, 848 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.32 (s, 3H), 1.36 (s, 3H), 2.54–2.58 (m, 1H), 2.76–2.80 (m, 1H), 2.87–2.96 (m, 2H), 2.54–2.58 (m, 1H), 4.01–4.09 (m, 3H), 4.29 (dd, *J* = 5.09, 12.8, 1H), 5.16 (d, *J* = 10.2, 1H), 5.26 (d, *J* = 18.1, 1H), 5.79–5.92 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.02, 26.5, 43.7, 52.9, 67.02, 71.4, 75.4, 81.1, 109.4, 117.1, 134.3; ESIMS *m/z* 237 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{11}H_{18}O_4Na$: 237.09735, found:237.09532.
(1S,2R)-1-(Allyloxy)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-ol (**12**): $[\alpha]_D^{25}$ +5 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 2925, 2856, 1458, 1375, 1218, 1070, 924 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.32 (s, 3H), 1.40 (s, 3H), 3.42–3.45 (m, 1H), 3.84–3.91 (m, 1H), 3.98–4.05 (m, 1H), 4.09–4.20 (m, 4H), 5.15–5.38 (m, 3H), 5.81–5.89 (m, 1H), 5.90–5.97 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 25.3, 26.5, 66.3, 72.1, 73.3, 75.8, 80.8, 109.1, 116.1, 117.5, 134.3, 137.5; ESIMS *m/z* 251 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{12}H_{20}O_4Na$: 251.12538, found: 251.12505.
(1S,2R)-1-(Allyloxy)-1-((S)-2,2-dimethyl-1,3-dioxolan-4-yl)but-3-en-2-yl acetate (**13**): $[\alpha]_D^{25}$ +20.4 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 3077, 2937, 1740, 1451, 1372, 1277, 1236, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 1.31 (s, 3H), 1.38 (s, 3H), 2.09 (s, 3H), 3.61 (t, 1H), 3.86–3.95 (m, 2H), 4.03–4.1 (m, 1H), 4.15–4.19 (m, 2H), 5.13–5.18 (m, 1H), 5.22–5.34 (m, 4H), 5.78–5.93 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.1, 25.4, 26.3, 65.3, 73.8, 74.1, 75.7, 76.7, 108.6, 117.3, 118.1, 133.2, 134.4, 169.8; ESIMS *m/z* 293 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{14}H_{22}O_5Na$: 293.13594, found: 293.13585.
(3R,4R,5S)-4-(Allyloxy)-5,6-dihydroxyhex-1-en-3-yl acetate (**14**): $[\alpha]_D^{25}$ +35 (*c* 0.5, $CHCl_3$); IR (KBr) ν_{max} 3435, 2932, 1733, 1374, 1247, 1087, 1024, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.15 (s, 3H), 3.45–3.54 (m, 2H), 3.62–3.68 (m, 1H), 3.72–3.78 (m, 1H), 4.06–4.17 (m, 2H), 5.13–5.40 (m, 4H), 5.48–5.52 (m, 1H), 5.80–6.0 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.09, 63.06, 70.4, 74, 74.2, 80.8, 117.6, 118, 133.4, 134.1, 171.1; ESIMS *m/z* 253 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{11}H_{18}O_5Na$: 253.10464, found: 253.10449.
(2S,3S,4R)-3-(Allyloxy)-1-(benzoyloxy)hex-5-ene-2,4-diyldiacetate (**15**): $[\alpha]_D^{25}$ +42 (*c* 0.1, $CHCl_3$); IR (KBr) ν_{max} 3085, 2988, 2937, 1745, 1646, 1427, 1373, 1233, 1024 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.03 (s, 3H), 2.09 (s, 3H), 3.74 (dd, *J* = 3.7, 7.3, 1H), 4.08–4.2 (m, 2H), 4.41 (dd, *J* = 5.6, 12.2, 1H), 4.65 (dd, *J* = 2.2, 12.2, 1H), 5.14–5.48 (m, 6H), 5.8–5.98 (m, 2H), 7.43 (t, *J* = 7.7, 2H), 7.55 (t, *J* = 7.5, 1H), 8.0 (d, *J* = 7.3, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.9, 20.1, 70.0, 73.1, 73.9, 78.4, 118, 118.7, 128.4, 129.5, 132.7, 133.1, 133.8, 166.1, 169.8, 170.05; ESIMS *m/z* 399 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{20}H_{24}O_7Na$: 399.14142, found: 399.14143.
(S)-2-Acetoxy-2-((2S,3R)-3-acetoxy-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate (**5**): white solid, mp 62–64 °C; $[\alpha]_D^{25}$ −163.5 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 2972, 1744, 1601, 1450, 1374, 1279, 1232, 1099, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.01 (s, 3H), 2.06 (s, 3H), 3.82–3.87 (m, 1H), 4.12–4.21 (m, 1H), 4.29–4.38 (m, 1H), 4.45 (dd, *J* = 5.09, 12.08, 1H), 4.7 (dd, *J* = 2.26, 12.08, 1H), 5.15–5.22 (m, 1H), 5.34 (ddd, *J* = 9.4, 5.0, 2.2, 1H), 5.91–6.0 (m, 1H), 6.03–6.12 (m, 1H), 7.43 (t, *J* = 7.5, 2H), 7.54 (t, *J* = 7.3, 1H), 8.0 (d, *J* = 7.17, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.7, 20.8, 62.2, 63.3, 65.9, 60.7, 73.8, 96.2, 122.5, 128.3, 129.7, 130.1, 131.9, 132.8, 165.6, 169.1, 169.9; ESIMS *m/z* 371 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{18}H_{20}O_7Na$: 371.11012, found: 371.11058.
(S)-2-Acetoxy-2-((2S,3R)-3-acetoxy-6-oxo-3,6-dihydro-2H-pyran-2-yl)ethyl benzoate (**1**); white solid, mp 130–134 °C; $[\alpha]_D^{25}$ −160.6 (*c* 1, $CHCl_3$); IR (KBr) ν_{max} 2929, 1743, 1602, 1450, 1373, 1278, 1229, 1102, 714 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): 2.02 (s, 3H), 2.09 (s, 3H), 4.5 (dd, *J* = 4.3, 12.4, 1H), 4.75 (dd, *J* = 9.8, 2.6, 1H), 4.93 (dd, *J* = 12.2, 2.2, 1H), 5.39 (dd, *J* = 6.0, 2.6, 1H), 5.48 (ddd, *J* = 9.6, 4.5, 2.4, 1H), 6.2 (d, *J* = 9.6, 1H), 6.9 (dd, *J* = 9.6, 6.0, 1H), 7.43 (t, *J* = 7.7, 2H), 7.55 (t, *J* = 7.5, 1H), 8.0 (d, *J* = 7.17, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 20.4, 20.6, 59.7, 61.9, 67.6, 75.4, 125.3, 128.4, 129.6, 133.2, 139.7, 161.05, 165.9, 169.4, 169.8; ESIMS *m/z* 385 $(M+Na)^+$; ESI-HRMS: *m/z* calcd for $C_{18}H_{18}O_8Na$: 385.08939, found: 385.08980.