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Total synthesis of (−)-cleistenolide

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ABSTRACT

The total synthesis of (−)-cleistenolide, a novel natural product recently isolated from the annonaceae species cleistochlamys kirkii oliver, is described. The synthesis proceeds starting from easily accessible D-manitol using a selective benzoylation, a selective acetonide deprotection, silylprotection and ring-closing metathesis reaction.

Naturally isolated 6-substituted-α,β-unsaturated-δ-lactones gained great attention of researchers due to their cytotoxic and anti-tumor properties.[1] In addition they inhibit HIV protease,[2] induce apoptosis,[3,4] and have proven to be anti-leukemic,[5] along with having many other relevant pharmacological properties.[6] Synargentolide A,[7] spicegerolide,[8] hyptolide,[9] synrotolide,[10] and anamarine[11] isolated from syncolostemon and hyptis species are examples of α,β-unsaturated-δ-lactones. Due to their pharmacological properties, these molecules became the interesting synthetic goals.

Cleistochlamys kirkii oliver is an annonaceae species occurring in Tanzania and Mozambique.[12] Extracts of this plant are used in traditional medicine as a remedy for the treatment of wound infections, rheumatism, and tuberculosis.[13] Recently, Nkunya coworkers[14] investigated the chemical composition of organic extracts from fruits, leaves, stem and root barks of C. kirkii oliver and discovered two novel plant constituents, which were named cleistenolide (**1**) and cleistodienol (**2**) (Fig. 1).[14] cleistenolide is known to possess antibacterial activity against *staphylococcus aureus* and *bacillus anthracis*, as well as antifungal activity against *Candida albicans*.

Recently, the first total synthesis of cleistenolide was published by Schmidt et al.[15] in overall 18% yield, by applying a ring-closing metathesis (RCM) protocol to prepare the key building block, an α,β-unsaturated lactone**.** Very recently synthesis of cleistenolide was reported by Cai et al. from the α,β-unsaturated acid through an intramolecular Yamaguchi esterification.[16]

Herein, we report the total synthesis of cleistenolide (**1**), starting from an enantiomerically pure D-manitol. Our synthesis confirms the absolute configuration assigned (−)-cleistenolide. As depicted in the retro synthetic analysis of the (−)-cleistenolide the crucial dihydropyran-2-one was prepared from ring-closing metathesis (RCM). Compound **4** would be prepared from benzoylated diacetonide **5**. Precursor **5** would be constructed from natural chiral template D-manitol **6** through the regioselective deprotection of acetonide, and monobenzoylation (Scheme 1).

The present synthesis commences (Scheme 2) from D-(+)-mannitol. The diol **7** is readily accessible from tri-*O*-isopropylidene-D-(+)-manitol,[18] with the terminal acetonides acting as

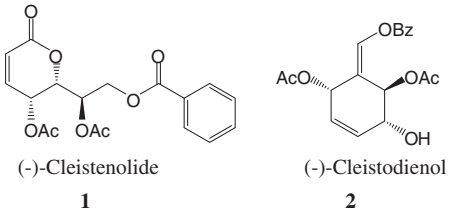
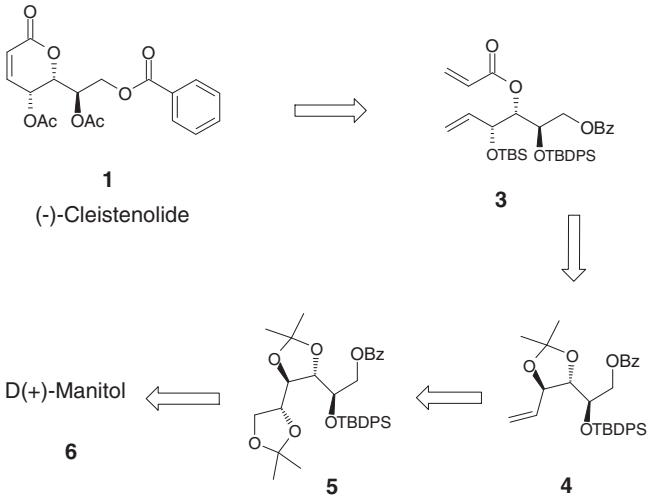


Figure 1. Chemical structures of cleistenolide (**1**) and cleistodienol (**2**).



Scheme 1. Retrosynthesis of (−)-cleistenolide.

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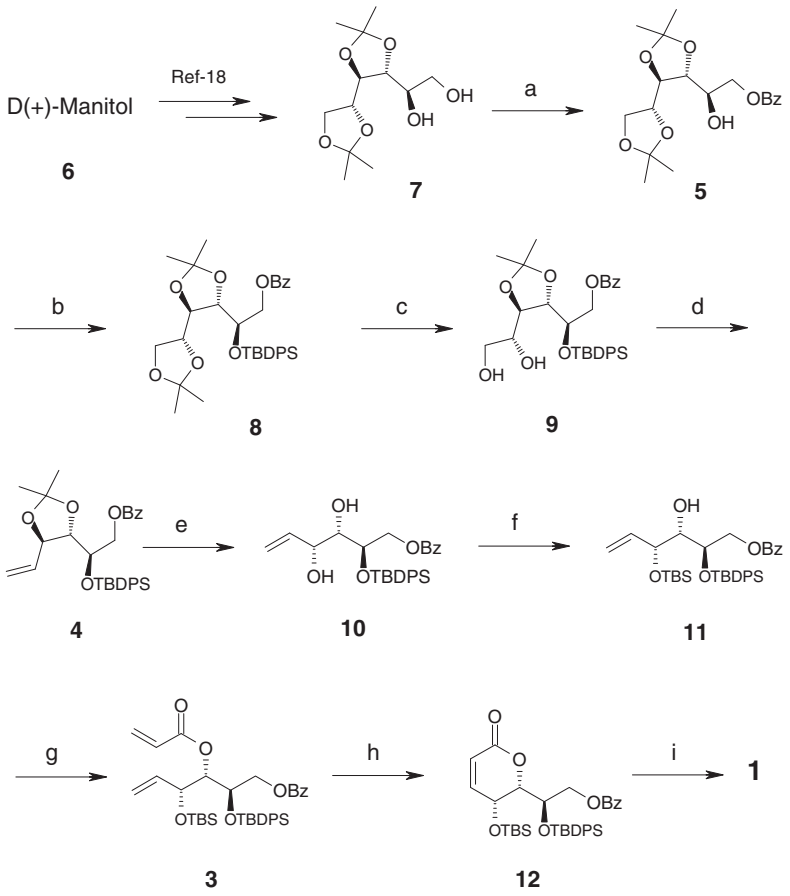
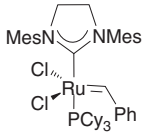


Scheme 2. Reagents and conditions: (a) Pyridine, benzoyl chloride, DMAP, CH_2Cl_2, −78–20 °C, 4 h, 83%; (b) TBDPS–Cl, imidazole, CH_2Cl_2, 0 °C to rt, 86%; (c) $CuCl_2{\cdot}2H_2O$, CH_3CN, 0 °C, 45 min, 99% (with recovered starting material); (d) PPh_3-imidazole-iodine, toluene, 110 °C, 4 h, 84%; (e) PPTS (cat)/MeOH, rt, 86% (or) $CuCl_2{\cdot}2H_2O$, CH_3CN, rt, 20 h, 84%; (f) TBS–OTf (1 equiv), 2,6-lutidine, CH_2Cl_2, −78 °C, 85%; (g) acryloyl chloride, DIPEA, CH_2Cl_2, 0 °C to rt, 81%; (h) 5 mol % Grubb's 2nd generation catalyst, toluene, 110 °C, 68%; (i) TBAF, THF then Ac_2O, 62%.

surrogates for the generation of olefin. The formation of the terminal diol **9** (Scheme 2) from the diacetonide **8** was achieved by the slight modification of a literature method.[18,19]

Monobenzoylation of diol **7** by using benzoyl chloride and DMAP in pyridine gave **5** in good yield.[19] The hydroxy group of compound **5** was protected with TBDPS–Cl to give silyl ether **8** with 86% yields. The diacetonide **8** underwent selective hydrolysis of the terminal acetonide using an equivalent amount of $CuCl_2{\cdot}2H_2O$ at 0 °C to generate the diol **9** in quantitative yield.[20] $Pb(OAc)_4$-cleavage of **9** followed by Wittig reaction provided the terminal olefin **4** in poor yield along with an unidentified mixture of products. However, it was smoothly converted **4** by the reaction with Ph_3P-imidazole-iodine in toluene and gave 84% yield.[21] Thus, acetonide cleavage of **4** by PPTS/MeOH (or) $CuCl_2{\cdot}2H_2O$ at room temperature produced the diol **10** (Scheme 2).[19]



2nd generation Grubb's catalyst

The key building block **10** is thus synthesized in a facile manner from D-(+)-mannitol in a combined 44% overall yield. The reaction of compound **10** on treatment with 1 equiv. of TBS–OTf, 2,6-lutidine, DCM, −78 °C selectively gave allylic silylether **11**, in 85% yield. Esterification of **11** with acryloyl chloride led to the formation of **3** in 81% yield. To avoid isomerization of the double bond by prolonged exposure to the reaction conditions, the reaction was arrested before complete disappearance of the starting material. Ring-closing metathesis of **3** proceeded well with 5 mol % of Grubbs catalyst. In dilute reaction conditions, the six-membered ring δ-lactone **12** was isolated in 68% yield (Scheme 2).[17,20b] Completion of the synthesis required desilylation of **12** and acetylation of the two secondary alcohols. This was most conveniently achieved as a one-flask reaction in THF by the addition of TBAF and subsequent addition of acetic anhydride. Notably, the desilylation/double acetylation proceeds in the absence of base and without any migration of the benzoyl group. Thus, analytically pure (−)-cleistenolide (**1**) was obtained as a single regio and stereoisomer in a yield of 62%. The physical and spectral data[22] of synthesised sample (−)-cleistenolide **1** were identical to those reported in the literature.[14,16] Our results, as well as Schmidt's report,[15] support the absolute configuration assigned to natural product as (−)-cleistenolide.

In summary, we have achieved the total syntheses of (−)-cleistenolide from a common precursor simply by changing the sequence of carbinol protection and thus allowing the formation of δ-lactone. Key features of present route to (−)-cleistenolide are the efficient utilization of the C_2-symmetry of the starting material (D-(+)-mannitol), a selective benzoylation, a selective acetonide deprotection, selective silyl protection and a ring-closing metathesis reaction.

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22. *Spectral data for selected compounds*: (*R*)-2-(*tert*-butyldiphenylsilyloxy)-2-((4*S*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl)ethylbenzoate (**4**): $[\alpha]_D^{25}$ −2.46 (*c* 1.4, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 1.36 (s, 3H), 1.39 (s, 3H), 3.86 (dd, 1H, *J* = 4.53, 3.39 Hz), 4.15 (dd, 1H, *J* = 6.79, 3.23 Hz), 4.22 (dd, 1H, *J* = 6.04, 5.66 Hz), 4.35 (dd, 1H, *J* = 7.93, 3.77 Hz), 4.45 (t, 1H, *J* = 7.36 Hz), 5.10 (d, 1H, *J* = 10.38 Hz), 5.30 (d, 1H, *J* = 17.18 Hz), 5.65 (ddd, 1H, *J* = 16.9, 10.57, 6.79 Hz), 7.30–7.50 (m, 8H), 7.62–7.78 (m, 7H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.2, 26.4, 26.6, 66.2, 69.8, 78.3, 79.5, 111.5, 119.2, 128.6, 129.4, 129.6, 130.0, 130.2, 134.2, 134.6, 165.9; IR (KBr): 3068, 2929, 2857, 1592, 1428, 1260, 1108 cm^{-1}; ESI-MS: *m*/*z* 553 [M$^+$+Na]; ESI-HRMS: *m*/*z* calcd for $C_{32}H_{38}O_5SiNa$: 553.2386, found: 553.2382.
(2R,3S,4R)-2-(tert-Butyldiphenylsilyloxy)-3,4-dihydroxyhex-5-enyl benzoate (**10**): $[\alpha]_D^{25}$ −4.24 (*c* 0.96, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9H), 2.22 (s, 1H), 2.65 (s, 1H), 3.58 (ddd, 1H, *J* = 8.80, 5.62, 2.80 Hz), 4.12 (dd, 1H, *J* = 9.44, 3.68 Hz), 4.32 (dd, 1H, *J* = 9.06, 3.02 Hz), 4.42 (dd, 2H, *J* = 7.36, 4.53 Hz), 5.18 (d, 1H, *J* = 10.57 Hz), 5.35 (d, 1H, *J* = 17.18 Hz), 5.80 (ddd, 1H, *J* = 16.9, 11.57, 6.42 Hz), 7.20–7.40 (m, 8H), 7.50 (t, 1H, *J* = 7.55 Hz), 7.70 (d, 4H, *J* = 6.61 Hz), 7.83 (d, 2H, *J* = 7.17 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 19.5, 26.7, 66.2, 71.4, 71.6, 78.8, 115.6, 128.4, 129.5, 130.0, 130.8, 133.4, 134.0, 138.6, 165.8; IR (KBr): 3068, 2929, 2857, 1592, 1428, 1260, 1108 cm^{-1}; ESI-MS: *m*/*z* 513 [M$^+$+Na]; ESI-HRMS: *m*/*z* calcd for $C_{29}H_{34}O_5SiNa$: 513.2073, found: 513.2069.
(2R,3S,4R)-4-(tert-Butyldimethylsilyloxy)-2-(tert-butyldiphenylsilyloxy)-3-hydroxyhex-5-enyl benzoate (**11**): $[\alpha]_D^{25}$ +26.4 (*c* 2.0, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.18 (s, 6H), 1.03 (s, 9H), 1.20 (s, 9H), 2.75 (d, 1H, *J* = 4.91 Hz), 3.68 (dd, 1H, *J* = 4.91, 4.70 Hz), 4.20 (dd, 1H, *J* = 6.40, 3.20 Hz), 4.45 (dd, 2H, *J* = 11.52, 5.09 Hz), 4.60 (dd, 1H, *J* = 9.25, 2.62 Hz), 5.20 (d, 1H, *J* = 10.57 Hz), 5.35 (d, 1H, *J* = 17.34 Hz), 5.80 (ddd, 1H, *J* = 17.56, 9.63, 7.36 Hz), 7.40–7.60 (m, 9H), 7.70 (t, 1H, *J* = 7.55 Hz), 7.82–7.95 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.3, −4.9, 18.6, 19.4, 25.9, 26.6, 66.2, 71.5, 71.9, 79.8, 115.7, 128.6, 129.4, 129.9, 130.08, 130.1, 134.0, 137.4, 165.9; IR (KBr): 3442, 2935, 2930, 1728, 1518, 1418, 1398, 1246, 1156, 836 cm^{-1}; ESI-MS: *m*/*z* 627 [M$^+$+Na]; ESI-HRMS: *m*/*z* calcd for $C_{35}H_{48}O_5Si_2Na$: 627.2432, found: 627.2435.
(2R,3S,4R)-3-(Acryloyloxy)-4-(tert-butyldimethylsilyloxy)-2-(tertbutyldiphenylsilyloxy)hex-5-enyl benzoate (3): $[\alpha]_D^{25}$ +56.5 (*c* 1.50, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.2 (s, 6H), 1.10 (s, 9H), 1.23 (s, 9H), 4.53 (dd, 1H, *J* = 7.55, 3.77 Hz), 4.62 (ddd, 2H, *J* = 11.33, 6.79, 4.53 Hz), 4.81 (dd, 1H, *J* = 8.30, 3.77 Hz), 5.43 (d, 1H, *J* = 9.80 Hz), 5.48 (dd, 1H, *J* = 6.04, 3.02 Hz), 5.58 (dd, 1H, *J* = 17.34, 3.77 Hz), 5.90 (ddd, 1H, *J* = 17.34, 9.82, 6.70 Hz), 6.20 (dd, 1H, *J* = 9.06, 3.02 Hz), 6.45 (dd, 1H, *J* = 10.57, 6.70 Hz), 6.75 (dd, 1H, *J* = 16.60, 3.02 Hz), 7.40–7.50 (m, 8H), 7.60 (t, 2H, *J* = 7.55 Hz), 7.70 (t, 2H, *J* = 7.55 Hz), 7.85 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −4.7, −5.2, 18.2, 19.5, 25.7, 26.8, 65.7, 69.0, 72.9, 73.3, 117.6, 127.8, 128.3, 129.6, 129.7, 129.8, 130.0, 131.9, 133.2, 134.1, 135.3, 164.9, 166.5; IR (KBr): 2949, 2895, 2854, 1727, 1535, 1423, 1240, 1198, 1154 cm^{-1}; ESI-MS: *m*/*z* 681 [M$^+$+Na]; ESI-HRMS: *m*/*z* calcd for $C_{38}H_{50}O_6Si_2Na$: 681.3043, found: 681.3047.
(R)-2-((2S,3R)-3-(tert-Butyldimethylsilyloxy)-6-oxo-3,6-dihydro-2H-pyran-2-yl)-2-(tert-butyldiphenylsilyloxy)ethyl benzoate (**12**): $[\alpha]_D^{25}$ −156 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.2 (s, 6H), 1.10 (s, 9H), 1.23 (s, 9H), 4.26 (dd, 1H, *J* = 9.77, 2.32 Hz), 4.29 (m, 1H), 4.47 (dd, 1H, *J* = 5.86, 2.22 Hz), 4.54 (dd, 1H, *J* = 12.56, 4.57 Hz), 4.86 (dd, 1H, *J* = 12.34, 2.32 Hz), 6.10 (d, 1H, *J* = 10.57 Hz), 6.93 (dd, 1H, *J* = 9.77, 5.80 Hz), 7.38–7.53 (m, 8H), 7.62 (t, 2H, *J* = 7.48 Hz), 7.73 (t, 1H, *J* = 7.48 Hz), 7.83–7.88 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ −5.2, −4.6, 18.0, 19.5, 25.6, 60.0, 66.0, 67.8, 80.0, 122.5, 128.4, 129.4, 129.6, 129.8, 133.3, 144.4, 162.8, 166.9; IR (KBr): 2939, 2855, 1717, 1505, 1423, 1248, 1148, 1054 cm^{-1}; ESI-MS: *m*/*z* 631 [M$^+$+H]]; ESI-HRMS: *m*/*z* calcd for $C_{36}H_{47}O_6Si_2$: 631.2906, found: 631.2909.
(−)-Cleistenolide (**1**): mp 130–133 °C; $[\alpha]_D^{25}$ −118 (*c* 0.5, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.03 (s, 3H), 2.09 (s, 3H), 4.52 (dd, 1H, *J* = 12.51, 4.40 Hz), 4.80 (dd, 1H, *J* = 9.60, 2.62 Hz), 4.93 (dd, 1H, *J* = 12.51, 2.22 Hz), 5.43 (dd, 1H, *J* = 6.02, 2.50 Hz), 5.51 (ddd, 1H, *J* = 9.50, 4.42, 2.32 Hz), 6.29 (d, 1H, *J* = 9.60 Hz), 7.00 (dd, 1H, *J* = 9.60, 6.10 Hz), 7.45 (t, 2H, *J* = 7.65 Hz), 7.57 (t, 1H, *J* = 7.42 Hz), 8.01 (d, 2H, *J* = 7.65 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 20.7, 59.7, 62.0, 67.7, 75.4, 125.3, 128.5, 129.6, 129.7, 129.7, 133.2, 139.7, 161.0, 166.0, 169.5, 169.9; IR (KBr): 2954, 1723, 1456, 1367, 1218, 1107, 1070; ESI-MS: *m*/*z* 385 [M$^+$+Na]; ESI-HRMS: *m*/*z* calcd for $C_{18}H_{18}O_8Na$: 385.0894, found: 385.0897.