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Stereoselective Total Synthesis of (−)-Cleistenolide

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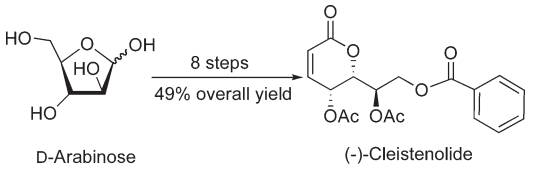


A facile stereoselective total synthesis of cleistenolide (**1**) from the natural chiral template D-arabinose has been achieved in eight steps and 49% overall yield, employing key steps including Wittig olefination, selective 1,3-*trans*-acetal formation, and modified Yamaguchi esterification.

The family Annonaceae includes over 2000 species,[1] quite a number of which have suffered species extinction before being well investigated. A considerable number of new compounds, having interesting chemical structures and important biological activities, have been isolated from this family.[2] In 2007, Nkunya et al.[3] discovered two novel constituents, cleistenolide (**1**) and cleistodienol (**2**) (Figure 1), from the Annonaceae, *Cleistochlamys kirkii* Oliver, a plant species found in Tanzania and Mozambique. Extracts made from this plant are used in traditional medicine as a remedy for treatment of wound infections, rheumatism, and tuberculosis.[4] Cleistenolide also reportedly exhibits in vitro antibacterial activity against *Staphylococcus aureus* and *Bacillus*

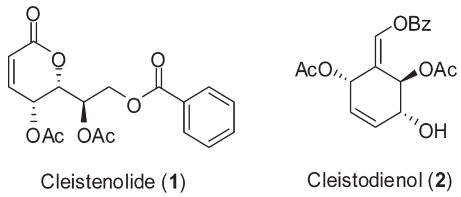
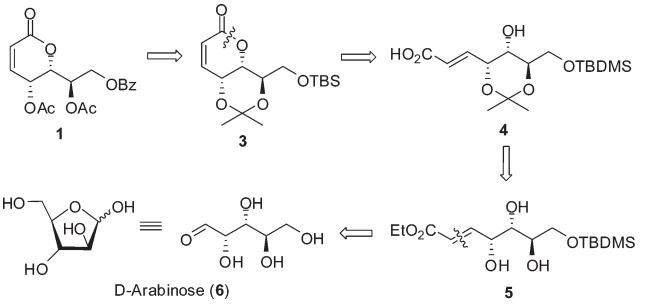


FIGURE 1. Chemical structures of cleistenolide (**1**) and cleistodienol (**2**).

anthracis, and antifungal activity against *Candida albicans*.[3] Recently, the first total synthesis of cleistenolide **1** was published by Schmidt and co-workers[5] in 18% overall yield, by applying a ring-closing metathesis (RCM) protocol to prepare the key building block, an α,β-unsaturated lactone.[6] Attracted by the potential pharmacological activity of cleistenolide, a knowledge of its absolute stereochemical configuration, and a shortage of the natural product (only 200 mg of cleistenolide can be extracted from 1 kg of dry plant), we launched a project aimed at the facile synthesis of cleistenolide **1**. Herein, we report the stereoselective total synthesis of cleistenolide by taking advantage of the chiral centers present in D-arabinose.

SCHEME 1. Retrosynthetic Analysis of Cleistenolide (1)



As depicted in the retrosynthetic analysis (Scheme 1), the crucial dihydropyran-2-one **3** was envisioned to be formed from the α,β-unsaturated acid **4** through an intramolecular Yamaguchi esterification.[7] Compound **4** would then be prepared from polyhydroxyl intermediate **5** through regioselective 1,3-*trans*-acetal formation[8] and subsequent ester−acid transformation. Precursor **5** would be constructed from natural chiral template D-arabinose (**6**) through regioselective silylation and Wittig olefination.[9]

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(2) For natural product isolated from Annonaceae species: (a) Nkunya, M.; Weenen, H.; Koyi, N.; Thijs, L.; Zwanenburg, B. *Phytochemistry* **1987**, *26*, 2563–2565. (b) Weenen, H.; Nkunya, M.; Mgani, Q.; Achenbach, H.; Posthumus, M.; Waibel, R. *J. Org. Chem.* **1991**, *56*, 5865–5867. (c) Kamperdick, C.; Van, N. H.; Sung, T. V. *Phytochemistry* **2002**, *61*, 991–994. (d) Li, C.; Lee, D.; Graf, T. N.; Phifer, S. S.; Nakanishi, Y.; Riswan, S.; Wani, M. C.; Oberlies, N. H. *J. Nat. Prod.* **2009**, *72*, 1949–1953.

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(5) Schmidt, B.; Kunz, O.; Biernat, A. *J. Org. Chem.* **2010**, *75*, 2389–2394.

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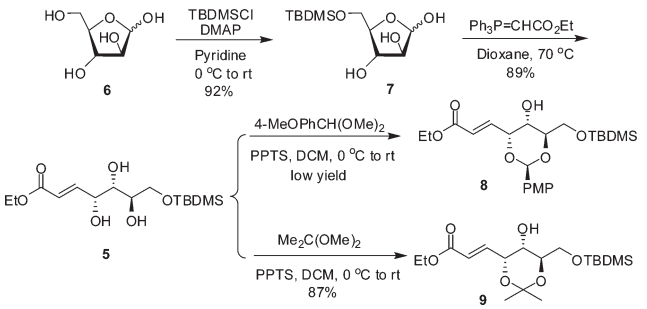
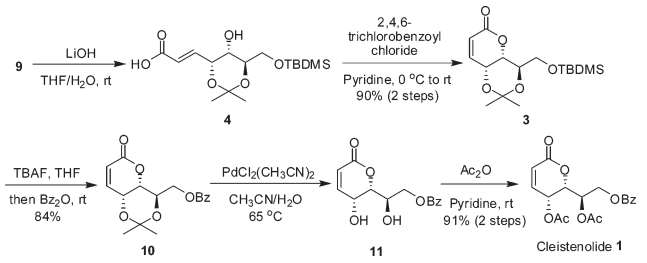
SCHEME 2. Synthesis of 1,3-Diol Protected Fragment 9



SCHEME 3. Synthesis of (−)-Cleistenolide (1)



Our synthesis (Schemes 2 and 3) started from D-arabinose. Treatment of D-arabinose **6** with TBDMSCl in pyridine at 0 °C regioselectively afforded the 5-*O*-silyl aldehyde **7** in a yield of 92%. Wittig olefination of aldehyde **7** with ethyl (triphenylphosphoranylidene)acetate[10] in dioxane at 70 °C furnished the α,β-unsaturated ester **5** in 89% isolated yield. The trans configuration (δ 6.16 ppm J = 15.7 Hz, =$CHCO_2Et$) was obtained with no cis product being observed in our reactions. On the basis of the literature precedent,[11] we initially attempted to synthesize 1,3-*trans*-*p*-methoxybenzylidene of compound **5** to differentiate the three chiral hydroxyl groups. However, reaction of **5** with 4-MeOPhCH-$(OMe)_2$ in the presence of PPTS in CH_2Cl_2 failed to generate the desired compound **8** in good yield. Fortunately, treatment of ester **5** with 2 equiv of $Me_2C(OMe)_2$ in the presence of a catalytic amount of PPTS at room temperature successfully afforded 1,3-*trans*-acetal, compound **9**, in 87% yield. The correct regioselectivity and relative stereochemistry of compound **9** were confirmed from its ^{13}C NMR spectrum, which showed chemical shifts at 24.74, 25.44, and 102.07 ppm, revealing it to be an *anti*-1,3-diol acetonide.[12]

Removal of ester protection from compound **9** with LiOH in THF/H_2O afforded the corresponding acid **4** in quantitative yield. Intramolecular esterification of acid **4** under modified Yamaguchi conditions[7] afforded key precursor **3** in 90% yield. The formation of **3** could be explained by thermal δ-lactonization through activation of carboxylic acid with 2,4,6-trichlorobenzoyl and subsequent pyridine-assisted addition−elimination. The *cis*-olefin configuration of **3** was confirmed by the correlated doublet (δ 6.19 ppm, J = 9.8 Hz, =$CHCO_2Et$) and the quartet (δ 6.79 ppm, J = 5.6, 9.8 Hz, RCHCH=) in its ^{1}HNMR spectrum. We were gratified that by using TBAF and Bz_2O in THF, the one-pot[5] desilylation and benzoylation of **3** proceeded smoothly affording compound **10** in high yield (84%). Removal of isopropylidene group from **10**, with bis(acetonitrile)dichloropalladium(II)[13,14] at 65 °C, furnished diol **11**. Acetylation, with Ac_2O in pyridine, completed the synthesis of (−)-cleistenolide (**1**) in 91% yield over the final two steps. The physical and spectral data of our synthetic sample **1** were in excellent agreement with the literature reports, except for the specific optical rotation. We observed a value of $[\alpha]^{25}_D$ −147 (*c* 0.4, $CHCl_3$), Schmidt and co-workers[5] reported $[\alpha]^{24}_D$ −165 (*c* 0.48, CH_2Cl_2), while Nkunya et al.[3] reported $[\alpha]_D$ −63.5 (*c* 0.7, $CHCl_3$) for the natural product. Our result, as well as Schmidt's report,[5] supports the absolute configuration assigned to natural product as (−)-cleistenolide.

In summary, we have accomplished the concise and stereoselective total synthesis of (−)-cleistenolide (**1**) in eight steps and 49% overall yield from D-arabinose. Our synthesis is very efficient with high stereoselectivities, indicating the powerful application of carbohydrates as chiral synthons. Key features of our strategy toward practical total synthesis of (−)-cleistenolide are the efficient combination of a Wittig olefination, selective 1,3-*trans*-acetal formation, and the use of modified Yamaguchi esterification.

Experimental Section

(4*R*,5*S*,6*R*,*E*)-Ethyl 7-(*tert*-Butyldimethylsilyloxy)-4,5,6-trihydroxyhept-2-enoate (5). To a solution of D-arabinose (1.50 g, 10.00 mmol) in pyridine (30 mL) was added *tert*-butyldimethylchlorosilane (1.65 g, 11.00 mmol) in the presence of a catalytic amount of DMAP at 0 °C under N_2 atmosphere. The mixture was allowed to warm to room temperature and stirred under these conditions for 12 h. The mixture was concentrated and the residue was purified by silica gel column chromatography with ethyl acetate as eluent to afford **7** (2.43 g, 92%) as a colorless syrup. To a solution of **7** (1.00 g, 3.78 mmol) in anhydrous dioxane (15 mL) was added (ethoxycarbonylmethylene)triphenylphosphorane (1.71 g, 4.92 mmol) under a N_2 atmosphere at room temperature. The mixture was stirred under these conditions for 2 h and then warmed to 70 °C and stirred for 5 h. The resulting clear solution was concentrated in vacuo, and the residue was poured into saturated aqueous NaCl (20 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 20 mL), and the combined organic phase was evaporated under reduced pressure to give a residue, which was subjected to the silica gel column chromatography (1:1 petroleum ether−ethyl acetate) to give **5** (1.12 g, 89%) as a colorless syrup: $[\alpha]^{25}_D$ +31 (*c* 1.2, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.09 (s, 6H), 0.89 (s, 9H), 1.28 (t, 3H, J = 7.1 Hz), 3.00 (br s, 2H), 3.35 (br s, 1H), 3.62−3.64 (m, 1H), 3.71 (dd, 1H, J = 5.4, 11.9 Hz), 3.76−3.81 (m, 2H), 4.18 (dd, 2H, J = 7.2, 14.3 Hz), 4.60 (s, 1H), 6.16 (d, 1H, J = 15.7 Hz), 7.00 (dd, 1H, J = 4.2, 15.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.5, 14.2, 18.2, 25.8, 60.5, 64.2, 70.5, 71.4, 73.7, 122.0, 147.4, 166.4. ESI(+)-MS calcd for $C_{15}H_{30}O_6Si$ 334.2 [M], found 357.1 [M + Na]$^+$. Anal. Calcd for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04. Found: C, 53.72; H, 9.15.

(*E*)-Ethyl 3-{(4*R*,5*S*,6*R*)-6-[(*tert*-Butyldimethylsilyloxy)methyl]-5-hydroxy-2,2-dimethyl-1,3-dioxan-4-yl}acrylate (9). To a mixture of **5** (245 mg, 0.73 mmol) and 2,2′-dimethoxypropane (0.18 mL, 1.46 mmol) in anhydrous CH_2Cl_2 (10 mL) at 0 °C was added PPTS

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(18.4 mg, 0.073 mmol). The mixture was stirred at room temperature for 10 h under N_2 atmosphere. Triethylamine (0.3 mL) was then added and the reaction mixture was concentrated to dryness. Purification of the remaining syrup by flash chromatography (4:1 petroleum ether−ethyl acetate) gave the acetonide **9** (238 mg, 87%) as a colorless syrup: $[\alpha]^{25}_D$ +97 (*c* 0.9, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9 H), 1.29 (t, 3H, J = 7.2 Hz), 1.34 (s, 3H), 1.44 (s, 3H), 2.04 (d, 1H, J = 5.4 Hz), 3.64−3.65 (m, 1H), 3.72 (dd, 1H, J = 6.0, 10.1 Hz), 3.84 (dd, 1H, J = 5.4, 10.2 Hz), 3.94−3.95 (m, 1H), 4.18−4.21 (m, 2H), 4.55 (s, 1H), 6.18 (d, 1H, J = 15.7 Hz), 7.00 (dd, 1H, J = 4.0, 15.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ −4.62, −4.60, 15.0, 19.0, 24.7, 25.4, 26.6, 61.2, 65.3, 71.4, 72.9, 75.2, 102.1, 123.1, 138.9, 143.8, 166.9. ESI(+)-MS calcd for $C_{18}H_{34}O_6Si$ 374.2 [M], found 397.1 $[M + Na]^+$. Anal. Calcd for $C_{18}H_{34}O_6Si$: C, 57.72; H, 9.15. Found: C, 57.57; H, 9.28.

(4*R*,4a*S*,8a*R*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-4,4a-dihydropyrano[3,2-*d*][1,3]dioxin-6(8a*H*)-one (3). To a solution of **9** (150 mg, 0.40 mmol) in THF (3 mL) was added 2 M aqueous LiOH (3 mL) dropwise and the reaction was stirred for 5 h at room temperature. Amberlite IR-120 (H^+) was then added to neutralize the solution and the mixture was poured into water (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). Evaporation of the combined organic phase followed by flash chromatography with (1:2 petroleum ether−ethyl acetate) gave acid **4** as colorless syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.39 (s, 3H), 1.40 (s, 3H), 3.60 (t, 1H, J = 6.9 Hz), 3.73 (dd, 1H, J = 6.0, 11.2 Hz), 3.77−3.81 (m, 2H), 4.48 (s, 1H), 6.05, (d, 1H, J = 15.5 Hz), 6.85 (dd, 1H, J = 4.4, 15.5 Hz). To a solution of **4** (67.5 mg, 0.19 mmol) in pyridine (2 mL) was added a solution of 2,4,6-trichlorobenzoyl chloride (0.052 g, 0.21 mmol) in CH_2Cl_2 (0.2 mL) at 0 °C and the reaction mixture was stirred at room temperature for 2 h. The reaction mixture was concentrated in vacuo to give a residue, which was subjected to the silica gel column chromatography (6:1 petroleum ether−ethyl acetate) to afford **3** (57.6 mg, 90% for two steps) as a colorless syrup: $[\alpha]^{25}_D$ −55 (*c* 0.5, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 6H), 0.90 (s, 9H), 1.41 (s, 3H), 1.43 (s, 3H), 3.83−3.89 (m, 3H), 4.28 (t, 1H, J = 5.2 Hz), 4.65 (t, 1H, J = 5.0 Hz), 6.19 (d, 1H, J = 9.8 Hz), 6.79 (dd, 1H, J = 5.6, 9.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ −5.3, −5.2, 18.3, 23.6, 24.7, 30.9, 59.2, 62.7, 72.2, 75.3, 101.9, 124.5, 139.8, 161.9. ESI(+)-MS calcd for $C_{16}H_{28}O_5Si$ 328.2 [M], found 351.2 $[M + Na]^+$. Anal. Calcd for $C_{16}H_{28}O_5Si$: C, 58.50; H, 8.59. Found: C, 58.32; H, 8.71.

{(4*R*,4a*S*,8a*R*)-2,2-Dimethyl-6-oxo-4,4a,6,8a-tetrahydropyrano-[3,2-*d*][1,3]dioxin-4-yl}methyl Benzoate (10). To a solution of **3** (152 mg, 0.46 mmol) in anhydrous THF (50 mL) was added TBAF (158 mg, 0.50 mmol). The mixture was stirred at room temperature for 30 min, then benzoic anhydride (416 mg, 1.80 mmol) was added and the reaction was stirred for an additional 8 h. The reaction was quenched by addition of water, and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phase was subsequently washed with aqueous NH_4Cl (50 mL) and saturated aqueous NaCl (50 mL), then dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by column chromatography (5:1 petroleum ether−ethyl acetate) gave **10** (123 mg, 84%) as a colorless syrup: $[\alpha]^{25}_D$ −15 (*c* 0.7, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 3H), 1.49 (s, 3H), 4.23 (ddd, 1H, J = 3.0, 5.5, 7.5 Hz), 4.40 (t, 1H, J = 4.5 Hz), 4.55 (dd, 1H, J = 6.0, 12.0 Hz), 4.59 (dd, 1H, J = 3.0, 12.0 Hz), 4.66 (dd, 1H, J = 4.5, 7.5 Hz), 6.22 (dd, 1H, J = 1.0, 10.0 Hz), 6.80 (dd, 1H, J = 5.5, 9.5 Hz), 7.45 (t, 2H, J = 8.0 Hz), 7.57 (t, 1H, J = 7.5 Hz), 8.04 (d, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 23.6, 24.5, 30.9, 59.1, 63.8, 69.8, 76.0, 102.4, 124.6, 128.4, 129.7, 130.2, 133.2, 133.6, 139.5, 161.2, 166.1. ESI(+)-MS calcd for $C_{17}H_{18}O_6$ 318.1 [M], found 341.1 $[M + Na]^+$. Anal. Calcd for $C_{17}H_{18}O_6$: C, 64.14; H, 5.70. Found: C, 63.87; H, 5.88.

Cleistenolide (1). A solution of **10** (55 mg, 0.17 mmol) in acetonitrile/water (30 mL, v/v 1:1) was heated at 65 °C in the presence of $PdCl_2(CH_3CN)_2$ (50 mg, 0.19 mmol) for 24 h. The mixture was cooled to room temperature and filtered through Celite. The filtrate was concentrated in vacuo to afford **11** as a syrup: ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.92 (br s, 1H), 3.56 (br s, 1H), 4.36−4.40 (m, 2H), 4.54 (d, 1H, J = 4.4 Hz), 4.59 (dd, 1H, J = 4.8, 12.3 Hz), 4.83 (dd, 1H, J = 1.2, 11.9 Hz), 6.18 (d, 1H, J = 9.7 Hz), 7.03 (dd, 1H, J = 5.9, 9.7 Hz), 7.46 (t, 2H, J = 7.6 Hz), 7.59 (t, 1H, J = 7.6 Hz), 8.05 (d, 2H. J = 7.9 Hz). ESI(+)-MS calcd for $C_{14}H_{14}O_6$ 278.1 [M], found 301.2 $[M + Na]^+$. Compound **11** was directly dissolved into a solution of acetic anhydride (1 mL) and pyridine (2 mL). After TLC indicated that all of the starting material was consumed, the solution was concentrated in vacuo, and the residue was subjected to the silica gel column chromatography (3:1 petroleum ether−ethyl acetate) to give **1** (56 mg, 91% for two steps) as a white crystal: mp 130−133 °C; $[\alpha]^{25}_D$ −147 (*c* 0.4, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$) δ 2.04 (s, 3H), 2.09 (s, 3H), 4.53 (dd, 1H, J = 12.5, 4.4 Hz), 4.80 (dd, 1H, J = 9.6, 2.5 Hz), 4.93 (dd, 1H, J = 12.5, 2.0 Hz), 5.42 (dd, 1H, J = 6.0, 2.5 Hz), 5.52 (ddd, 1H, J = 9.5, 4.0, 2.3 Hz), 6.29 (d, 1H, J = 9.7 Hz), 7.00 (dd, 1H, J = 9.6, 6.1 Hz), 7.45 (t, 2H, J = 7.6 Hz), 7.57 (t, 1H, J = 7.4 Hz), 8.02 (d, 2H. J = 7.7 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 20.5, 20.7, 59.7, 62.0, 67.7, 75.5, 125.4, 128.5, 129.6, 129.7, 129.7, 133.3, 139.7, 161.1, 166.0, 169.5, 169.9. HR-ESI(+)-MS calcd for $C_{18}H_{18}O_8$ 362.1002 [M], found 385.0896 $[M + Na]^+$, 401.0636 $[M + K]^+$.

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Supporting Information Available: Spectral data for compounds **1**, **3**, **4**, **5**, **7**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.