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Stereoselective Total Synthesis of (–)-Cleistenolide

Chao Cai^{§,†}, Jun Liu[§], Yuguo Du^{§,†}, and Robert J. Linhardt[‡]

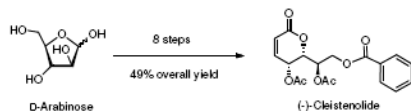
Yuguo Du: duyuguo@rcees.ac.cn; Robert J. Linhardt: linhar@rpi.edu

[§] State Key Laboratory of Environmental Chemistry and Ecotoxicology, Research Center for Eco-Environmental Sciences, Chinese Academy of Sciences, Beijing 100085, China

[†] College of Chemistry and Chemical Engineering, Graduate University of Chinese Academy of Sciences, Beijing 100049, China

[‡] Departments of Chemistry, Biology, and Chemical and Biological Engineering, Rensselaer Polytechnic Institute, Troy, New York 12180

Abstract



A facile stereoselective total synthesis of cleistenolide (**1**) from 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 anthracis*, and antifungal activity against *Candida albicans*.³ Recently, the first total synthesis of cleistenolide **1** was published by Schmidt and co-workers⁵ 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 advantages of the chiral centers present in D-arabinose.

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 regio-selective 1,3-*trans*-acetal formation⁸ and subsequent ester-acid

Correspondence to: Yuguo Du, duyuguo@rcees.ac.cn; Robert J. Linhardt, linhar@rpi.edu.

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

transformation. Precursor **5** would be constructed from natural chiral template D-arabinose (**6**) through regioselective silylation and Wittig olefination.⁹

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)acetate¹⁰ 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, =CHCO₂Et) was obtained with no *cis* product being observed in our reactions. Based on 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 CH₂Cl₂ failed to generate the desired compound **8** in good yield. Fortunately, treatment of ester **5** with 2 equivalents of Me₂C(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 ¹³C NMR spectrum, which showed chemical shifts at 24.74, 25.44, and 102.07 ppm, revealing it to be an *anti*-1,3-diol acetone.¹²

Removal of ester protection from compound **9** with LiOH in THF/H₂O afforded the corresponding acid **4** in quantitative yield. Intramolecular esterification of acid **4** under modified Yamaguchi conditions⁷ 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, =CHCO₂Et) and the quartet (δ 6.79 ppm, J = 5.6, 9.8 Hz, RCHCH=) in its ¹H NMR spectrum. We were gratified that by using TBAF and Bz₂O in THF, the one-pot⁵ desilylation and benzylation 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 Ac₂O 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 $[\alpha]_D^{25}$ –147 (*c* 0.4, CHCl₃), Schmidt and co-workers⁵ reported $[\alpha]_D^{24}$ –165 (*c* 0.48, CH₂Cl₂), while Nkunya et al.,³ reported $[\alpha]_D$ –63.5 (*c* 0.7, CHCl₃) 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 towards 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), *tert*-butyldimethylchlorosilane (1.65 g, 11.00 mmol) was added in the presence of catalytic amount of DMAP at 0 °C under N₂ 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), (ethoxycarbonylmethylene)triphenylphosphorane (1.71 g, 4.92 mmol) was added under a N₂ 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 CH₂Cl₂ (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: $[\alpha]^{25}_{\text{D}} +31$ (*c* 1.2, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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 C₁₅H₃₀O₆Si: 334.2 [M]; found 357.1 [M+Na]⁺. Anal. Calcd for C₁₅H₃₀O₆Si: 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 CH₂Cl₂ (10 mL) at 0 °C PPTS (18.4 mg, 0.073 mmol) was added. The mixture was stirred at room temperature for 10 h under N₂ 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: $[\alpha]^{25}_{\text{D}} +97$ (*c* 0.9, CHCl₃); ¹H NMR (600 MHz, CDCl₃): δ 0.08 (s, 3H), 0.09 (s, 3H), 0.90 (s, 9H), 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); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₈H₃₄O₆Si: 374.2 [M]; found 397.1 [M+Na]⁺. Anal. Calcd for C₁₈H₃₄O₆Si: C, 57.72; H, 9.15. Found: C, 57.57; H, 9.28.

(4*R*,4*aS*,8*aR*)-4-[(*tert*-Butyldimethylsilyloxy)methyl]-2,2-dimethyl-4,4*a*-dihydropyrano[3,2-*d*][1,3]dioxin-6(8*aH*)-one (3**)**

To a solution of **9** (150 mg, 0.40 mmol) in THF (3 mL), 2 M aqueous LiOH (3 mL) was added 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 CH₂Cl₂ (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: ¹H NMR (500 MHz, CDCl₃): 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) a solution of 2,4,6-trichlorobenzoyl chloride (0.052 g, 0.21 mmol) in CH₂Cl₂ (0.2 mL) at 0 °C was added 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: $[\alpha]^{25}_{\text{D}} -55$ (*c* 0.5, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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 C₁₆H₂₈O₅Si: 328.2 [M]; found 351.2 [M+Na]⁺. Anal. Calcd for C₁₆H₂₈O₅Si: C, 58.50; H, 8.59. Found: C, 58.32; H, 8.71.

{{(4*R*,4*aS*,8*aR*)-2,2-Dimethyl-6-oxo-4,4*a*,6,8*a*-tetrahydro pyrano[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) TBAF (158 mg, 0.50 mmol) was added. 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 NH₄Cl (50 mL) and saturated aqueous NaCl (50 mL), then dried over anhydrous Na₂SO₄, and concentrated *in vacuo*. Purification by column chromatography (5:1 petroleum ether-ethyl acetate) gave **10** (123 mg, 84%) as a colorless syrup: $[\alpha]_D^{25}$ -15 (*c* 0.7, CHCl₃); ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): 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 C₁₇H₁₈O₆: 318.1 [M]; found 341.1 [M + Na]⁺. Anal. Calcd for C₁₇H₁₈O₆: 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 PdCl₂(CH₃CN)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: ¹H NMR (500 MHz, CDCl₃): 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 C₁₄H₁₄O₆: 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; $[\alpha]_D^{25}$ -147 (*c* 0.4, CHCl₃); ¹H NMR (600 MHz, CDCl₃): 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); ¹³C NMR (150 MHz, CDCl₃): 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 C₁₈H₁₈O₈: 362.1002 [M]; found: 385.0896 [M + Na]⁺, 401.0636 [M + K]⁺.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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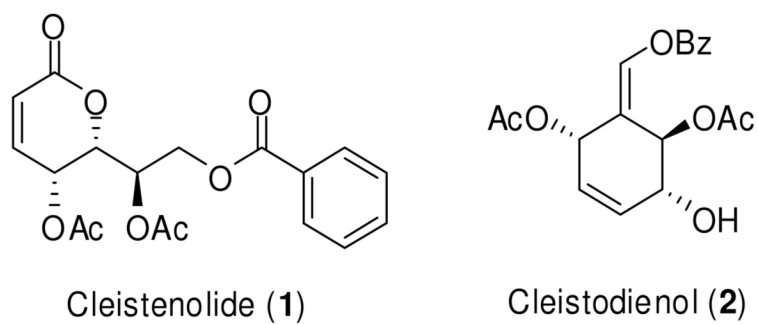
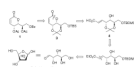
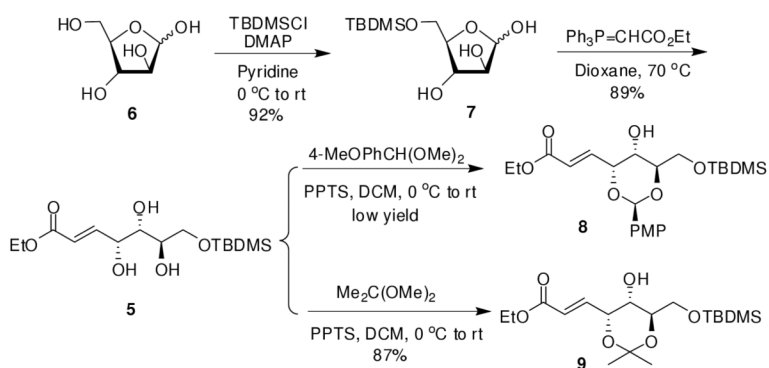
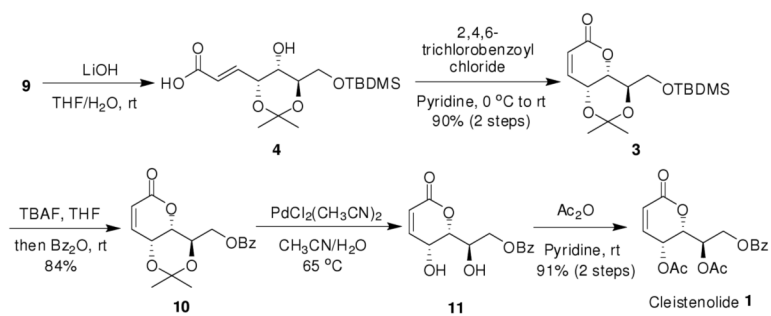


FIGURE 1.
Chemical structures of cleistenolide (1) and cleistodienol (2)

**SCHEME 1. Retrosynthetic Analysis of Cleistenolide (1)**

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

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