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A concise total synthesis of cleistenolide

A. Bal Reddy, B. Kumara Swamy, Jhillu Singh Yadav *

Centre for Semiochemicals Division, CSIR-Indian Institute of Chemical Technology, Hyderabad 500607, India

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ABSTRACT

A concise total synthesis of cleistenolide has been achieved from D-glucose. The synthesis of cleistenolide proceeds in six steps from D-glucose diacetonide in 42.5% overall yield. Selective benzoylation and Still-Gennari olefination are the key reactions involved in the synthesis.

1. Introduction

Cleistochlamys kirkii Oliver extracts are used as a remedy in traditional medicine for treatment of wound infections, rheumatism, and tuberculosis.[1] In 2007, Nkunya et al. reported on two novel constituents; cleistenolide and cleistodienol, from the plant extracts of the *Cleistochlamys kirkii* Oliver[2] family of Annonaceae. Cleistenolide exhibit a wide range of biological activities such as antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, and antifungal activity against *Candida albicans* (Fig. 1).[3]

There are several reports on the total synthesis of cleistenolide[4] using different methods such as ring closing metathesis, selective acylation, *cis*-olefination,[4a,c] Yamaguchi lactinization[4b] mixed hydride reduction and Still-Gennari olefination[4e] as the key steps.

As part of our longstanding interest in the synthesis of bioactive natural products, we have taken up the total synthesis of cleistenolide. Recently we reported[5] the synthesis of cleistenolide from commercially available D-mannitol. Herein, we report short synthesis of cleistenolide in 6 steps without changing chiral centers present in the starting material, D-glucose diacetonide.

2. Results and discussion

The retrosynthetic analysis (−)-cleistenolide indicated that it could be synthesized by *cis*-olefination followed by lactonization with the corresponding aldehyde **3**. Aldehyde **3** can be prepared from compound **4** via selective acetonide deprotection followed by cleavage of the diol using $NaIO_4$. Diacetylated compound **4** can be easily accessed from compound **5** (D-glucose diacetonide) by selective acetonide deprotection, and benzoylation[6] using a dibutyltinoxide complex with a catalytic amount of DMAP and acetic anhydride (Scheme 1).

The synthesis of target molecule **1** began with commercially available D-glucose diacetonide **5**. The selective acetonide deprotection of D-glucose diacetonide **5** with 60% acetic acid and water over 8 h gave triol **6** in 85% yield. Selective benzoylation[6] with benzoyl chloride using dibutyltin oxide complex in the presence of a catalytic amount of DMAP afforded **7** in 72% yield.

Compound **7** was converted into diacetylated **4** by using acetic anhydride and pyridine in DCM at 0 °C for 2 h to furnish compound **4** in 92% yield. Compound **4** was further treated with trifluoroacetic acid and water (2:1) at 25 °C for 3 h to give the product in 95% yield as a 12:1 epimeric mixture of lactol **8**. Oxidative cleavage of **8** with sodium periodate[7] in an acetone and water mixture gave aldehyde **3**. Aldehyde **3** was subjected directly to a one pot homologation followed by lactonization reaction using Still-Gennari[8] olefination conditions to achieved the title compound (−)-cleistenolide **1** in 82% overall yield (Scheme 2). The physical and spectroscopic data ($[\alpha]_D^{25}$, ^1H and ^{13}C NMR.) of compound **1** were identical with the reported data in the literature.[4]

3. Conclusion

In summary, we have demonstrated the concise, efficient and economic synthetic route for the total synthesis of cleistenolide. The key steps involved in this synthesis are selective benzoylation and Still-Gennari olefination. The total synthesis of cleistenolide has been achieved in six steps with an overall yield of 42.5%.

4. Experimental

4.1. General

Air and/or moisture sensitive reactions were carried out in anhydrous solvents under an argon atmosphere in an oven or flame-dried glassware. All anhydrous solvents were distilled prior to use: THF, from Na and benzophenone; CH_2Cl_2, DMSO from CaH_2.

* Corresponding author. Fax: +91 40 27160512.
E-mail address: yadavpub@gmail.com (J.S. Yadav).

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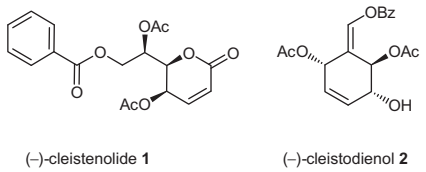
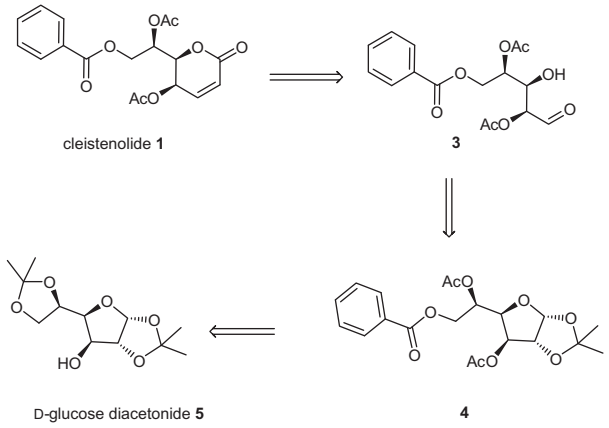
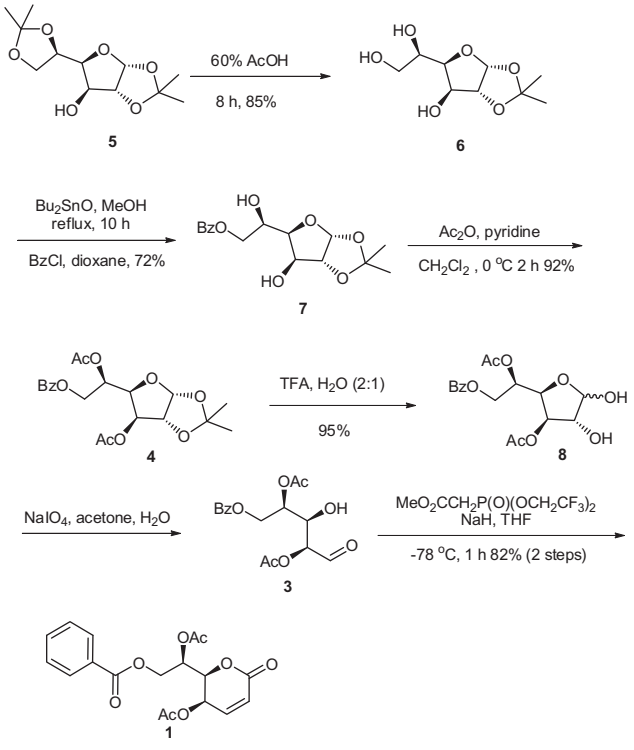


(–)-cleistenolide **1** (–)-cleistodienol **2**

Figure 1.



Scheme 1. Retrosynthetic analysis of (−)-cleistenolide **1**.



Scheme 2. Total synthesis of (−)-cleistenolide **1**.

Commercial reagents were used without purification. Column chromatography was carried out by using ACME silica gel (60–120 mesh). Optical rotations $[\alpha]_D$ are given in $10^{-1} \circ cm^2\ g^{-1}$. Infrared spectra were recorded in $CHCl_3$/neat (as specified) on Perkin-Elmer 683 spectrometer. ^1H and ^{13}C NMR spectra were recorded on a Varian Unity-500 or a Bruker-300 spectrometer. Chemical shifts (δ) are given in ppm relative to TMS and coupling constants (J) in Hz. Mass spectra were obtained on an Exactive Thermo Scientific Orbitrap Mass Spectrometer. The following abbreviations are used to designate signal multiplicity: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, td = triplet of double, q = quartet, m = multiplet, br = broad.

4.2. (*R*)-1-((3a*R*,5*R*,6*S*,6a*R*)-6-Hydroxy-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethane-1,2-diol 6

D-Glucose diacetonide **5** (10 g 38.4 mmol) was dissolved in a mixture of acetic acid (100 mL) and water (50 mL). The mixture was stirred for 12 h at 25 °C. The crude was concentrated under vacuum at 50 °C. A pure compound was obtained by recrystallization from ethyl acetate to give triol compound **6** (7.2 g, 32.64 mmol, 85%).$[\alpha]_D^{20} = -11.2$ (*c* 1.1, H_2O); IR (KBr): 3420, 2952, 2795, 1434, 1322, 1275, 1235, 1095, 1043 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ 1.32 (s, 3H), 1.47 (s, 3H), 3.62 (dd, J = 6.0, 11.7 Hz, 1H), 3.79 (dd, J = 3.0, 11.8 Hz, 1H), 3.90–3.94 (m, 1H), 4.04 (dd, J = 2.6, 8.3 Hz, 1H), 4.22 (d, J = 2.3 Hz, 1H), 4.51 (d, J = 3.4 Hz, 1H), 5.90 (d, J = 3.4 Hz, 1H). ^{13}C NMR (75 MHz, CD_3OD): δ 26.4, 27.0, 65.3, 70.4, 75.5, 81.3, 86.5, 106.4, 112.7. HRMS (ESI-MS): m/z $[M+Na]^+$ calcd for $C_9H_{16}O_6Na$: 243.0845; found: 243.0850.

4.3. (*R*)-2-Hydroxy-2-((3a*R*,5*R*,6*S*,6a*R*)-6-hydroxy-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethyl benzoate 7

To a mixture of Bu_2SnO (7.92 g, 31.8 mmol) and triol compound **6** (7.0 g, 31.8 mmol) dry methanol (210 mL) was added. The mixture was heated at reflux for 10 h. The solvent was evaporated and residue was dried under vacuum. The crude product was dissolved in 1,4-dioxane (210 mL), after which were added benzoyl chloride (4.92 g, 35.0 mmol) and DMAP (0.1 mol equiv). The mixture was left for 12–16 h and the reaction was monitored by TLC. The mixture was concentrated in vacuo at 40 °C. The tin compounds were removed on silica gel column chromatography by eluting with $CHCl_3$, and a pure compound was obtained by ethyl acetate elute to give mono 6-*O*-benzoylated **7** 7.4 g (22.9 mmol, 72%). $[\alpha]_D^{20} = +7.1$ (*c* 1.05, $CHCl_3$); IR (KBr): 3485, 2952, 2795, 1690, 1275, 1235, 1075, 1029 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s,3H), 1.48 (s, 3H), 3.11 (d, J = 3.8 Hz, 1H), 3.20 (d, J = 3.2 Hz, 1H), 4.19 (dd, J = 3.0, 6.8 Hz, 1H), 4.33–4.40 (m, 1H), 4.41–4.43 (m, 1H), 4.50 (dd, J = 6.04, 11.3 Hz, 1H), 4.56 (d, J = 3.78, 1H), 5.99 (d, J −3.8, 1H), 7.45 (t, J = 7.4, 2H), 7.57 (t, J = 7.4 Hz, 1H), 8.05 (d, J = 7.1 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 24.9, 25.5, 66.0, 66.5, 73.3, 79.3, 84.5, 104.5, 111.0, 127.6, 128.8, 132.4, 132.8, 166.4. HRMS (ESI-MS): m/z $[M+H]^+$ calcd for $C_{16}H_{21}O_7$: 325.1287; found: 325.1281.

4.4. (*R*)-2-Acetoxy-2-((3a*R*,5*R*,6*S*,6a*R*)-6-acetoxy-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-5-yl)ethyl benzoate 4

Pyridine (4.87 g. 61.6 mmol) was added to a stirred solution of mono 6-*O*-benzoylated **7** (5.0 g, 15.4 mmol) and CH_2Cl_2 (50.0 mL) at 0 °C. The mixture was stirred at 0 °C for 10 min, after which Ac_2O (3.93 g, 38.5 mmol) was added to the mixture at 0 °C and stirred for 2 h at 0 °C. The reaction was monitored by TLC, and the solvents were removed under vacuum at 40 °C. The residue was dissolved in CH_2Cl_2 (50.0 mL) and sat. $NaHCO_3$ solution (30 mL) was added. Organic layer was separated and concentrated under reduced pressure. The crude was subjected to column chromatography by eluting with hexanes and ethyl acetate obtained 5.75 g of compound **4** (14.1 mmol, 92%). $[\alpha]_D^{20} = +5.6$ (*c* 1.01, $CHCl_3$); IR (KBr): 3465, 2932, 2791, 1690, 1685, 1670, 1097, 1042 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ 1.32 (s, 3H), 1.53 (s, 3H), 2.01 (s, 3H),

2.08 (s, 3H), 4.40 (dd, J = 6.0, 12.1 Hz, 1H), 4,52 (d, J = 3.8 Hz, 1H), 4.55 (d, J = 3.0 Hz, 1H), 4.80 (dd, J = 2.3, 12.8 Hz, 1H), 5.35–5.47 (m, 2H), 5.96, (d, J = 3.8 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 7.53–7.60 (t, J = 7.6 Hz, 2H), 8.03 (d, J = 7.1 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.7, 20.8, 26.2, 26.7, 64.0, 67.5, 74.8, 76.8, 83.2, 105.1, 112.5, 128.4, 129.6, 129.7, 133.1, 166.1, 169.6, 169.8. HRMS (ESI-MS): m/z $[M+H]^+$ calcd for $C_{20}H_{25}O_9$: 409.1499; found: 409.1494.

4.5. (*R*)-2-Acetoxy-2-((2*R*,3*R*,4*R*,5*S*)-3-acetoxy-4,5-dihydroxytetrahydrofuran-2-yl)ethyl benzoate 8

A solution of compound **4** (0.9 g, 2.2 mmol) in a mixture of TFA: H_2O (2:1, 27 mL) was stirred at 25 °C for 3 h, and monitored by TLC. TFA was evaporated under reduced pressure and codistilled with benzene to afford 0.77 g of compound **8** as a thick syrup (2.09 mmol, 95%). ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.01 (s, 3H), 2.08 (s, 3H), 4.10 (m, 1H), 4.40 (dd, J = 6.04, 12.8 Hz, 1H), 4.58 (dd, J = 3.8, 9.1 Hz, 1H), 4.76 (dd, J = 2.7, 12.1 Hz, 1H), 5.21–5.40 (m, 2H), 5.56 (d, J = 4.5 Hz, 1H), 7.42 (t, J = 7.6 Hz, 2H), 7.53–7.60 (m, 1H), 8.02 (d, J = 6.8 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.6, 20.8, 26.4, 26.7, 64.2, 67.4, 74.8, 76.7, 83.2, 105.2, 128.4, 129.7, 129.8, 133.1, 166.3, 169.7, 169.8. HRMS (ESI-MS): m/z $[M+Na]^+$ calcd for $C_{17}H_{20}O_9Na$: 391.1006; found: 391.1004.

4.6. (*R*)-2-Acetoxy-2-((2*S*,3*R*)-3-acetoxy-6-oxo-3,6-dihydro-2*H*-pyran-2-yl)ethyl benzoate 1

Compound **8** (0.1 g, 0.27 mmol) was dissolved in acetone–water (9:1, 10 mL). $NaIO_4$ (0.07 g, 3.1 mmol) was added at 0 °C. The reaction mixture was stirred for 30 minutes at 0 °C, after which acetone was removed under vacuum at 40 °C. Water (10 mL) was added to the above crude and extracted with ethyl acetate (2 × 10 mL). The ethyl acetate layer was concentrated under vacuum and dried; this crude was used for next step without purification.

To a stirred solution of sodium hydride 60% (23 mg, 0.57 mmol) in THF (5 mL) at −78 °C was added $MeO_2CCH_2P(O)(OCH_2CF_3)_2$ (0.18 g, 0.57 mmol) and the mixture was stirred 30 min at −78 °C. To this solution the above crude aldehyde **3** was added at −78 °C and the reaction was stirred for 2 h at −78 °C. Water was then added and the compound was extracted with ethyl acetate (2 × 10 mL). Pure product was obtained by column chromatography by eluting with hexanes and ethyl acetate to afford 0.075 g of compound **1** (0.22 mmol, 82%). Mp 132–134 °C. $[\alpha]_D^{25}$ = −153.1 (c 0.8, $CHCl_3$); IR (neat): 2975, 1739, 1475, 1385, 1260, 1115, 1045, 752 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.04 (s, 3H), 2.09 (s, 3H),4.52 (dd, J = 4.5, 12.7 Hz, 1H), 4.80 (dd, J = 2.5, 9.6 Hz, 1H), 4.92 (dd, J = 2.3, 12.7 Hz, 1H), 5.41 (dd, J = 2.6, 6.0 Hz, 1H), 5.51 (ddd, J = 2.3, 4.4, 9.6 Hz, 1H), 6.28 (d, J = 9.6 Hz, 1H), 7.00 (dd, J = 6.0, 9.6 Hz, 1H), 7.45 (t, J = 7.4 Hz, 2H), 7.56 (t, J = 7.4 Hz, 1H), 8.01 (d, J = 7.2 Hz, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 20.5, 20.7, 59.7, 62.1, 67.7, 75.6, 125.4, 128.4, 129.6, 129.7, 133.2, 139.8, 161.1, 165.9, 169.5, 169.8. ESI-MS: m/z: 363 $(M+H)^+$. HRMS calcd for $C_{18}H_{19}O_8$: 363.1080; found: 363.1089.

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References

1. Nkunya, M. H. H. *Pure Appl. Chem.* **2005**, *77*, 1943.
2. Verzar, R.; Petri, G. *J. Ethnopharmacol.* **1987**, *19*, 67.
3. Samwel, S.; Mdachi, S. J. M.; Nkunya, M. H. H.; Irungu, B. N.; Moshi, M. J.; Moulton, B.; Luisi, B. S. *Nat. Prod. Commun.* **2007**, *2*, 737.
4. (a) Schmidt, B.; Kunz, O.; Biernat, A. *J. Org. Chem.* **2010**, *75*, 2389; (b) Cai, C.; Liu, J.; Du, Y.; Linhardt, R. J. *J. Org. Chem.* **2010**, *75*, 5754; (c) Babu, D. C.; Ashalatha, K.; Rao, C. B.; Selavam, J. J.; Venkateswarlu, Y. *Helv. Chem. Acta* **2011**, *94*, 2215; (d) Ramesh, P.; Meshram, H. M. *Tetrahedron Lett.* **2011**, *52*, 2443; (e) Ghogare, R. S.; Wadavrao, S. B.; Narsaiah, A. V. *Tetrahedron Lett.* **2013**, *54*, 5674.
5. Reddy, B. V. S.; Reddy, B. P.; Pandurangam, T.; Yadav, J. S. *Tetrahedron Lett.* **2011**, *52*, 2306.
6. Tsuda, Y.; Nishimura, M.; Kobayashi, T.; Sato, Y.; Kanemitsu, K. *Chem. Pharm. Bull.* **1991**, *39*, 2883.
7. Markad, S. D.; Karanjule, N. S.; Sharma, T.; Sabharwal, S. G.; Dhavale, D. D. *Org. Biomol. Chem.* **2006**, *4*, 3675.
8. Still, W. C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405.