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New antitumour agents with α,β-unsaturated δ-lactone scaffold: Synthesis and antiproliferative activity of (−)-cleistenolide and analogues

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ABSTRACT

A stereoselective total synthesis of (−)-cleistenolide (**1**) from D-glucose has been achieved. This new approach for the synthesis of (−)-cleistenolide and analogues involves a one-*C*-atom degradation of the chiral precursor, (*Z*)-selective Wittig olefination, followed by the final δ-lactonisation. Synthesized compounds showed potent growth inhibitory effects against selected human tumour cell lines, especially 2,4,6-trichlorobenzoyl derivative **12**, which in the culture of MDA-MB 231 cells displayed the highest activity (IC_{50} 0.02 μM) of all compounds under evaluation. A preliminary SAR study reveals the structural features that are beneficial for antiproliferative activity of synthesized δ-lactones, such as presence of either electron-withdrawing or electron-donating substituents in the aromatic ring, as well as the presence of cinnamoyl functionality instead of benzoyl group at the O-7 position.

Natural products and their synthetic derivatives are important as drug candidates or lead structures for the discovery of novel drugs.[1] Natural products possessing α,β-unsaturated δ-lactone ring, have long been considered as attractive scaffolds in drug discovery because of their diverse array of biological activities such as antibacterial, antifungal, and antitumour properties.[2] Recently Nkunya et al. isolated the α,β-unsaturated δ-lactone (−)-cleistenolide (**1**, Scheme 1) from the *Cleistochlamys kirkii* Oliver, and found that it displays significant antibacterial activity against *Staphylococcus aureus* and *Bacillus anthracis*, as well as antifungal activity toward *Candida albicans*.[3] Due to its interesting structural features and evident pharmacological potential, the synthesis of cleistenolide has attracted much attention among synthetic medicinal chemists. Eight total syntheses of (−)-cleistenolide have been reported so far, all of them using a chiral pool strategy and D-mannitol,[4] D-arabinose,[5] (−)-isoascorbic acid,[6] or D-tartaric acid[7] as starting materials. Moreover, a chemoenzymatic approach to (−)-6-*epi*-cleistenolide was also recently reported.[8] Despite the existence of these synthetic pathways, there still exists a need to develop novel procedures for this class of compounds. In continuation of our ongoing studies on the synthesis of bioactive natural products from abundant monosaccharides,[9] we have focused on the synthesis of (−)-cleistenolide because of its potential antitumour activity. Namely, despite the existence of numerous compounds with α,β-unsaturated δ-lactone scaffold that exhibited strong antitumour activities in vitro,[10] there is no record in the literature about antiproliferative activities of **1** or its analogues. Herein, we disclose a new total synthesis of (−)-cleistenolide starting from D-glucose, along with the preparation of several new mimics of **1** bearing electron-withdrawing or electron-donating substituents in the aromatic ring. A new analogue of **1** in which a cinnamoyl moiety replaces benzoyl group at the C-7 position was also designed, since the cinnamoates represent a well known class of anticancer agents.[11] A brief study of in vitro antitumour activity of synthesized compounds against a panel of human cancer cell lines is an additional objective of this work.

As depicted in the retrosynthetic analysis (Scheme 1), the required dihydropyran-2-one **1** was envisioned to be formed from the (*Z*)-enoate **2a** through an intramolecular transesterification process. Intermediate **2a** would be prepared from fully protected glucofuranose derivative **2b** through initial acetal deprotection, subsequent glycol cleavage and final (*Z*)-selective Wittig (or Horner–Wadsworth–Emmons) olefination. Finally, precursor **2b** can be prepared from commercially available monoacetone D-glucose

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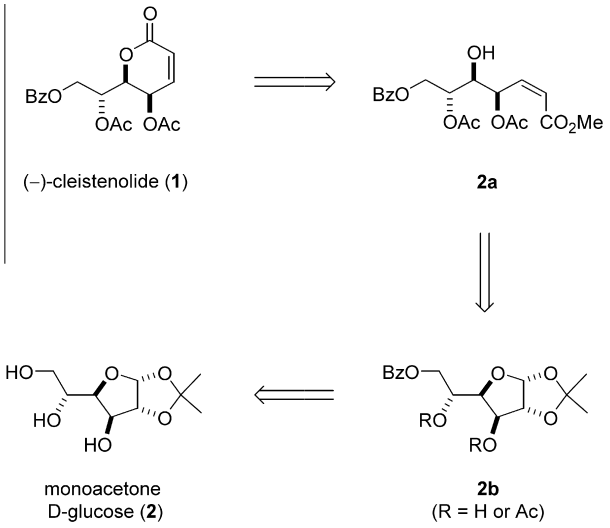
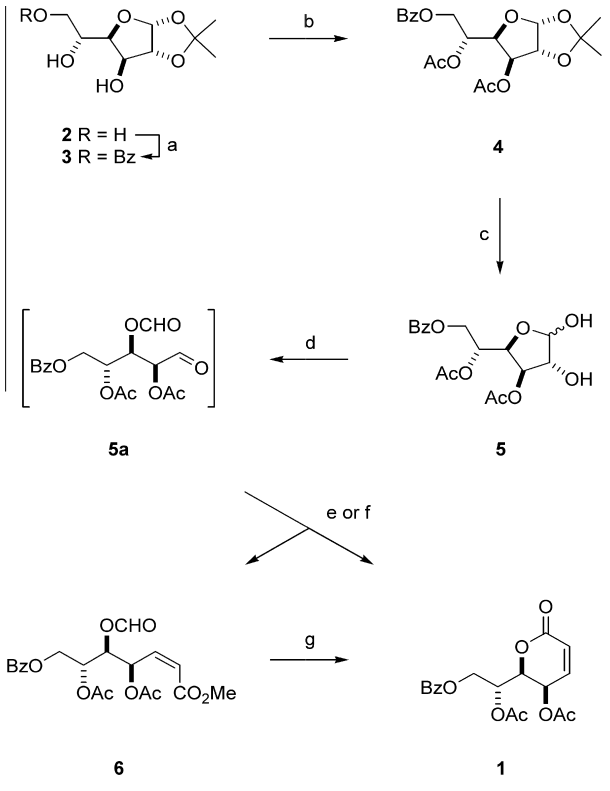


Scheme 1. Retrosynthetic analysis of (–)-cleistenolide (**1**).

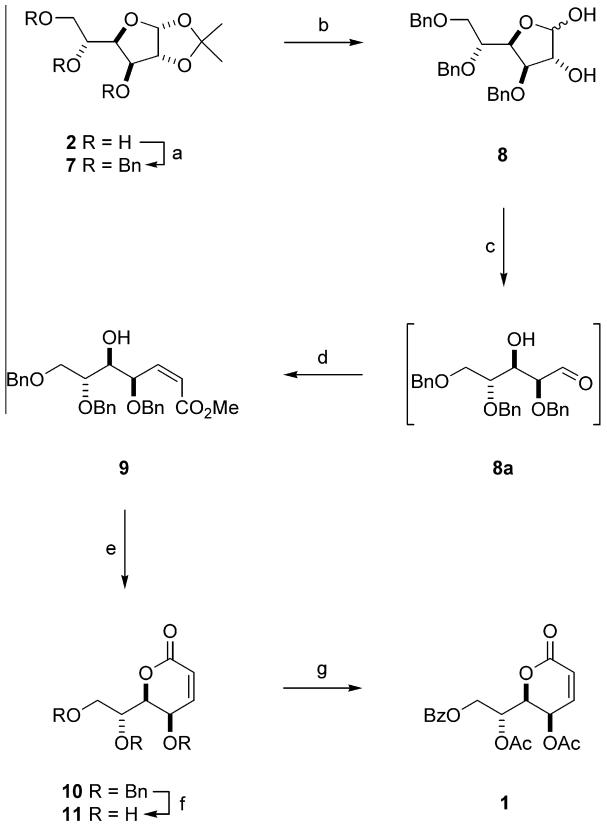
(**2**) through regioselective 6-O-monobenzoylation and subsequent 3,5-di-O-acetylation.[12]

The first synthetic route to (–)-cleistenolide (**1**) started from commercially available monoacetone D-glucose **2** (Scheme 2), which was treated with benzoyl chloride in the presence of pyridine in dichloromethane using a slightly modified literature procedure.[12] The known[13] 6-*O*-benzoyl derivative **3** was obtained in 75% yield. Treatment of **3** with acetic anhydride in a mixture of dry pyridine and dichloromethane, gave fully protected intermediate **4** in 98% yield. Physical constants of thus prepared products **3** and **4** were in full agreement with the reported values {compound **3**: mp 198–199 °C (EtOAc/hexane), lit.[13a] mp 195–196 °C (EtOH/$CHCl_3$), $[\alpha]_D$ = +6.0 (EtOH, *c* 1.0), lit.[13a] $[\alpha]_D$ = +4.7 (EtOH, *c* 0.5); compound **4**: mp 108 °C (EtOH), lit.[14] mp 108 °C (EtOH), $[\alpha]_D$ = +5.5 ($CHCl_3$, *c* 1.0); lit.[14] $[\alpha]_D$ = +7.1 ($CHCl_3$, *c* 3.0)}. IR, NMR and HRMS data for both **3** and **4** are consistent with their structures. Hydrolytic removal of the isopropylidene protecting group in **4** gave the expected lactol **5** in 84% yield. Oxidative cleavage of lactol **5** with periodic acid, followed by *Z*-selective Wittig olefination[15] of the resulting aldehyde **5a** with stabilized C_2-ylide ($Ph_3P{=}CHCO_2Me$) afforded a mixture of the unsaturated ester **6** (4%) and target **1** (10%). Prolonging the reaction time and elevating the reaction temperature did not increase the yields of Wittig olefination. Slightly better yields of both products **6** and **1** were obtained, when the olefination step was carried out in the presence of Still's reagent[16] derived from unstable ylide using the *Z*-selective Horner–Wadsworth–Emmons reaction protocol.[17] Under these conditions, *Z*-enoate is obtained as the main reaction product (25%), accompanied with minor amounts of target **1** (13%). Treatment of **6** with toluene-4-sulfonic acid in wet pyridine gave 64% yield of natural product **1**. This procedure provided the target **1** in 17.9% overall yield from six synthetic steps. The physical and spectral data of thus obtained synthetic sample **1** were in excellent agreement with the literature reports.[12]

In order to develop a more efficient procedure for the preparation of (–)-cleistenolide (**1**) we envisioned an alternative seven-step route which is shown in Scheme 3. The sequence also started from monoacetone D-glucose **2**, which was converted to the known[18] tri-*O*-benzyl ether **7** under the standard conditions,[12]



Scheme 2. Reagents and conditions: (a) BzCl, 1:1 CH_2Cl_2/Py, rt, 4 h, 75%; (b) Ac_2O, 1:1 CH_2Cl_2/Py, rt, 20 h, 98%; (c) 90% aq TFA, CH_2Cl_2, 0 °C, 0.5 h, then rt for 2 h, 84%; (d) H_5IO_6, EtOAc, 4.5 h; (e) Ph_3P:$CHCO_2Me$, Et_3N, MeOH, N_2, 0 °C, 2.5 h, 4% of **6** (from **5**), 10% of **1** (from **5**); (f) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$, NaH, THF, Ar, −10 °C, 3 h, 25% of **6** (from **5**), 13% of **1** (from **5**); (g) TsOH, aq Py, rt, 5 days, 64% of **1**.



Scheme 3. Reagents and conditions: (a) BnBr, NaH, DMF, 0 °C, 0.5 h, then rt for 2 h, 97%; (b) 50% aq TFA, rt for 18 h, 83%; (c) H_5IO_6, EtOAc, H_2O, rt, 3 h; (d) Ph_3P:$CHCO_2Me$, MeOH, 0 °C, 1 h, rt, 22 h, 84% (from **8**); (e) TsOH, CH_2Cl_2, rt, 96 h, 94%; (f) $FeCl_3$, CH_2Cl_2, rt, 24 h, 64%; (g) (i) BzCl, Py, CH_2Cl_2, rt, 4 h; (ii) Ac_2O, rt, 20 h, 81%.