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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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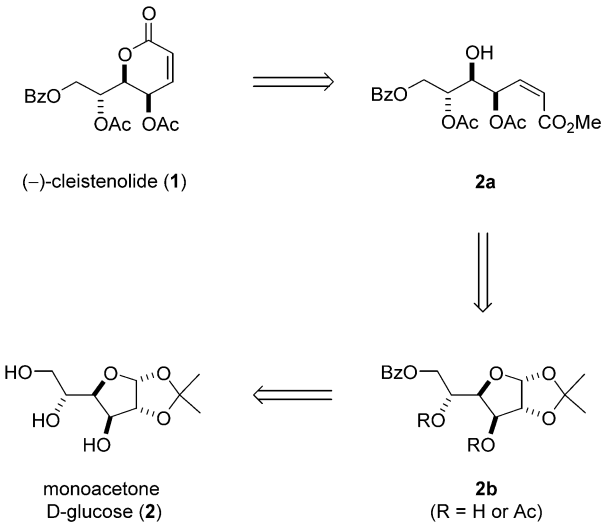
ABSTRACT

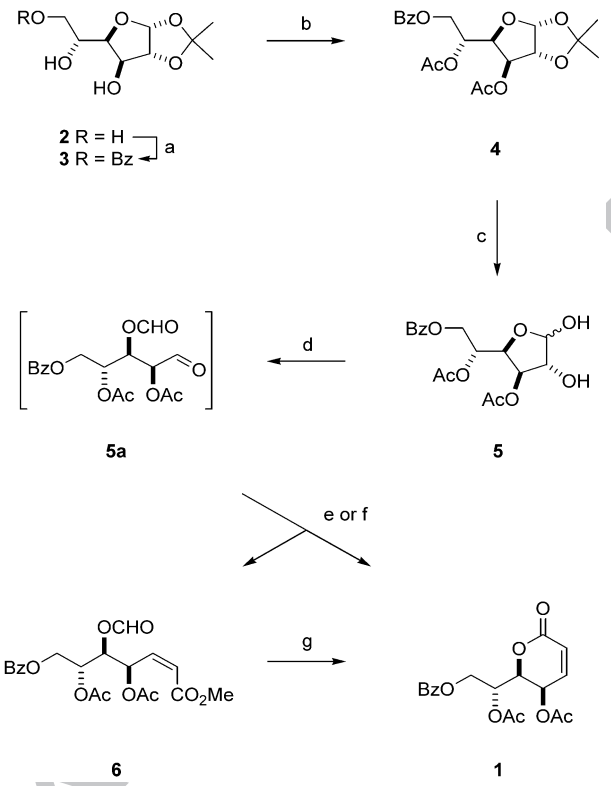
A stereoselective total synthesis of (−)-cleistenolide (**1**) from D-glucose has been achieved. This new approach for the synthesis of (−)-cleistenolide and analogues involves a one-C-atom degradation of the chiral precursor, (*Z*)-selective Wittig olefination, followed by the final δ-lactonisation. 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 anti-fungal 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 (**2**) through regioselective 6-*O*-monobenzoylation and subsequent 3,5-di-*O*-acetylation.[12]



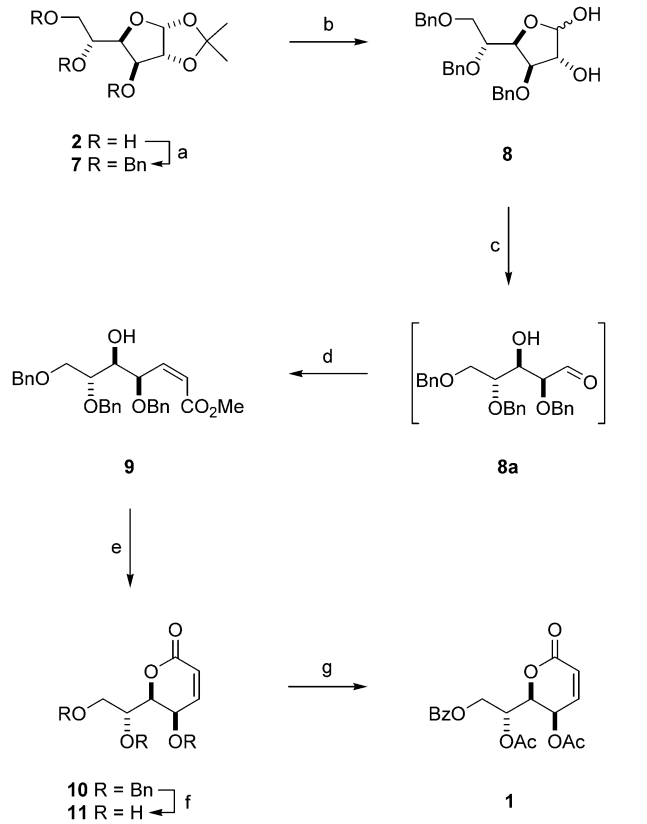
Scheme 1. Retrosynthetic analysis of (−)-cleistenolide (**1**).



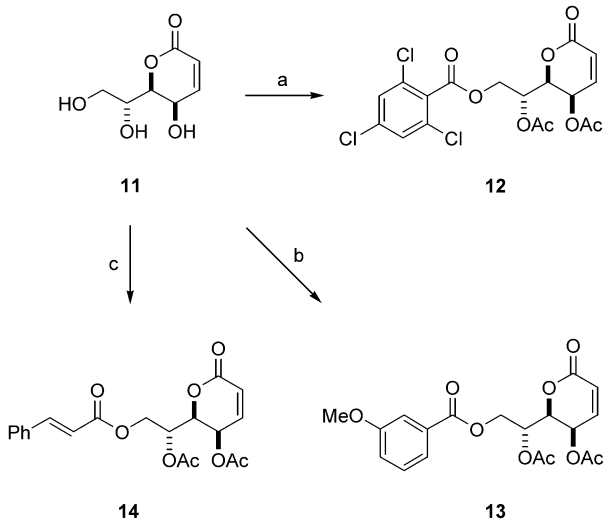
Scheme 2. Reagents and conditions: (a) BzCl, 1:1 CH_2Cl_2/Py, rt, 4 h, 75%; (b) Ac_2O, 1:1 CH_2Cl_2/Py, rt, 20 h, 98%; (c) 90% aq TFA, CH_2Cl_2, 0 °C, 0.5 h, then rt for 2 h, 84%; (d) H_5IO_6, EtOAc, 4.5 h; (e) Ph_3P:$CHCO_2Me$, Et_3N, MeOH, N_2, 0 °C, 2.5 h, 4% of **6** (from **5**), 10% of **1** (from **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**.

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] 7-*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-sulphonic 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] and in an almost quantitative yield. Rather different optical



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%.



Scheme 4. Reagents and conditions: (a) (*i*) 2,4,6-trichlorobenzoyl chloride, Py, CH_2Cl_2, rt, 4 h; (*ii*) Ac_2O, rt, 20 h, 85%; (b) (*i*) 3-methoxybenzoyl chloride, Py, CH_2Cl_2, rt, 6 h; (*ii*) Ac_2O, rt, 20 h, 67%; (c) (*i*) cinnamoyl chloride, Py, DMAP, CH_2Cl_2, rt, 4 h; (*ii*) Ac_2O, rt, 20 h, 35%.

rotations are reported in the literature for **7** {lit.[18] $[\alpha]_D$=−61.8 (*c* 0.3, $CHCl_3$); lit.[19] $[\alpha]_D$=−33.0 (*c* 9.3, $CHCl_3$)} and both of these values are different from our value {$[\alpha]_D$=−45.2 (*c* 1.0, $CHCl_3$)}. Such different optical rotation values can be caused by differences in the concentration and by the measurement temperature. By contrast, ^{1}H NMR data of **7** were in reasonable agreement with the reported values.[18,19] Additionally, IR, ^{13}C NMR and HRMS data are in full agreement with structure **7**. Hydrolytic removal of the isopropylidene protective group in **7** (50% aq TFA), gave the corresponding lactol **8** (83%). This is followed by oxidative cleavage of **8** with periodic acid, and by subsequent *Z*-selective Wittig olefination of the resulting aldehyde **8a**. We assume that the low yield observed during the conversion of lactol **5** into enoate **6** (Scheme 2) is a consequence of the enhanced stability of intermediate **5a**, which contains two electron-withdrawing groups at both adjacent positions to the formyl group. In order to avoid the formation of formyl ester, the oxidative step was carried out in aqueous ethyl acetate,[20] to afford the corresponding aldehyde **8a**. Wittig reaction of crude **8a** with a stabilized C_2-ylide (Ph_3P=$CHCO_2Me$) gave (*Z*)-enoate **9** in 84% yield. Treatment of **9** with toluene-4-sulphonic acid in dichloromethane (rt, 96 h) gave an excellent yield of pyranone **10** (94%). Compound **10** was subsequently treated with $FeCl_3$ in anhydrous dichloromethane to afford the expected triol **11** in 64% yield.[21] Finally, the *O*-benzoyl protection of primary alcohol **11** followed by the acetylation of secondary hydroxyls gave the target molecule (−)-cleistenolide (**1**). This procedure provided the target **1** in 33% overall yield from seven synthetic steps. It further means that this new approach to **1** provided the highest overall yield and the least number of synthetic steps than the majority of previously published syntheses (seven of eight). The single exception is the synthesis from D-arabinose,[5] which provided a total yield of 49% from eight synthetic steps. The spectroscopic and physical data (IR, ^{1}H and ^{13}C NMR spectra, optical rotation and melting point) of synthesized natural product **1** were identical in all respects to the data reported in the literature.[12] An additional advantage of this new approach is that it provides access not only to the natural product **1**, but also to a variety analogues of **1** for biological testing. Therefore, our next studies are directed to prepare analogues with additional electron-withdrawing and electron-donating substituents in the aromatic ring (**12** and **13**, Scheme 4), as well as a new analogue of **1** in which cinnamoyl moiety replaces benzoyl group at the C-7 position (**14**).

One-pot procedure involving trichlorobenzoylation of primary hydroxyl group in **11**, followed by the acetylation of secondary hydroxyl groups (Py, CH_2Cl_2), provides the required analogue **12** in 85% yield. Similarly, reaction of **11** with 3-methoxybenzoyl chloride, followed by acetylation under the similar conditions afforded a 67% yield of analogue **13**. Finally, the cinnamoyl protection of primary alcohol **11** followed by the acetylation of secondary hydroxyl groups (Py, DMAP, CH_2Cl_2) provided a moderate yield of target **14** (35%).

The biological activities of the synthesized natural product **1**, and the corresponding analogues **12**–**14** were evaluated by an in vitro cytotoxicity test carried out with a panel of eight human tumour cell lines including myelogenous leukaemia (K562), promyelocytic leukaemia (HL-60), T cell leukaemia (Jurkat), Burkitt's lymphoma (Raji), ER^+ breast adenocarcinoma (MCF-7), ER^- breast adenocarcinoma (MDA-MB-231), cervix carcinoma (HeLa), lung adenocarcinoma epithelial cells (A549) and one normal cell line (foetal lung fibroblasts MRC-5). Cell growth inhibition was evaluated after 72-h cells treatment by MTT asay.[22] The commercial antitumour agent doxorubicin (DOX) was used as the positive control in this assay.

As shown in Table 1, natural product **1**, and the corresponding mimics **12**–**14** exhibit moderate to potent in vitro anticancer activities, with maximal activities in the submicromolar range. The natural product **1** and analogues **13** and **14** were completely inactive toward normal MRC-5 cells, in contrast to the commercial drug DOX that showed a potent cytotoxic activity toward these cells (IC_{50} 0.10 μM). Only analogue **12** exhibited a weak cytotoxicity against this cell line (IC_{50} 45.68 μM). All three analogues **12**–**14** demonstrated potent antiproliferative effects

Table 1. In vitro cytotoxicities of (−)-cleistenolide (**1**), the corresponding analogues **12**–**14** and DOX

Compounds	IC_{50} (μM) [a]								
	K562	HL-60	Jurkat	Raji	MCF-7	MDA-MB 231	HeLa	A549	MRC-5
1	7.65	1.21	14.22	36.94	26.07	2.25	7.32	16.34	>100
12	1.02	36.21	6.25	11.24	0.62	0.02	14.02	4.23	45.68
13	2.69	0.89	8.31	25.64	4.71	7.46	1.95	11.02	91.34
14	0.28	24.59	0.25	11.21	15.98	1.46	0.21	2.02	>100
DOX	0.25	0.92	0.03	2.98	0.20	0.09	0.07	4.91	0.10

[a] IC_{50} is the concentration of compound required to inhibit the cell growth by 50% compared to an untreated control. The values are means of three independent experiments done in quadruplicates. Coefficients of variation were <10%.

toward K562 cells in the low micromolar range. The most active compound is 7-*O*-cinnamoyl derivative **14** that displayed 27-fold higher potency when compared to lead **1** and showed similar activity as DOX in the culture of these cells. The highest potency in the culture of HL-60 cells was recorded after treatment with **13** (IC_{50} 0.89 μM), which is similar to that observed for the commercial drug doxorubicin (IC_{50} 0.92 μM) as well as for the parent compound **1** (IC_{50} 1.21 μM) in the same cell line. Cinnamoate **14** is the most active analogue against Jurkat cells. It is 57-fold more potent than natural product **1** in the same cell culture, but was over 8-fold less active then DOX against this cell line. Raji cells are the least sensitive to lead **1**. Analogues **12** and **14** are the most potent compounds against this malignant cell line, being approximately 3-fold more active than **1** and almost 4-times less active than DOX. Trichlorobenzoyl derivative **12** showed the highest potency toward MCF-7 cells (IC_{50} 0.62 μM). It exhibited 42-fold stronger activity with respect to lead **1** and approximately 3-times lower potency when compared to DOX. The parent compound **1** and all synthesized analogues (**12**–**14**) exhibited notable antiproliferative effects on MDA-MB 231 cells, with IC_{50} values in the low-micromolar range. The most active molecule against this cell line is 7-*O*-trichlorobenzoyl derivative **12** (IC_{50} 0.02 μM) being over 100-fold more potent than **1**. In the same time, molecule **12** exhibited 4.5-fold higher potency than DOX in this cell line. Additionally, this molecule represents the most active compound synthesised in this work. (−)-Cleistenolide (**1**) and analogues **12**–**14** demonstrated diverse antiproliferative effects toward HeLa cells in the range of IC_{50} 0.21–14.02 μM. The highest potency in the culture of these cells was recorded after treatment with **14** (IC_{50} 0.21 μM), which was approximately 35-fold more active than lead **1**. However, comparing to DOX, this analogue exhibited 3-fold lower activity against HeLa cells. The most potent (−)-cleistenolide mimic toward the A549 cell line is compound **14**, that exhibited over 8 and 2.5-fold higher potency when compared to lead **1** and DOX, respectively.

As the data in Table 1 further reveal the introduction of either three electron-withdrawing groups (such as Cl) or an electron-donating group (such as OMe), in the aromatic ring of **1**, improved antiproliferative activity of the analogue against the majority of tumour cell lines under evaluation (the exemptions are HL 60, MDA-MB-231 and HeLa cells). Replacement of the C-7 benzoyl group in **1** by a cinnamate moiety caused similar effects. Namely, the cinnamic isostere of **1** (analogue **14**) showed the increased antitumour potency against seven of eight tumour cell lines under evaluation (except against HL-60 cells).

In conclusion, a facile stereoselective total synthesis of (−)-cleistenolide (**1**) from the commercially available chiral template diacetone D-glucose (**2**) has been achieved employing one-*C*-atom degradation of the chiral precursor **2**, (*Z*)-selective Wittig olefination, and the subsequent δ-lactonisation as key steps. The final *O*-benzoyl protection of primary alcohol group, followed by the acetylation of secondary hydroxyls gave the target molecule **1** in seven steps and 33% overall yield. The same experimental methodology provided an access to three novel (−)-cleistenolide mimics (compounds **12**, **13** and **14**) for biological testing. Natural product **1** showed moderate to potent in vitro anticancer activities against the all human malignant cell lines under evaluation. The highest potency of **1** was recorded in the culture of HL-60 cells (IC_{50} 1.21 μM), which is similar to that observed for the commercial drug doxorubicin (IC_{50} 0.92 μM). This is the first record in the literature on antitumour activity (−)-cleistenolide. So far this molecule was known only by its antibacterial and antifungal activity. Generally, analogues **12**–**14** appeared to be more potent than lead **1**. With the exception of HL-60, MDA-MB 231 and HeLa cells, all of the remaining cell lines were more sensitive to analogues **12**–**14** than to lead **1**. Certain compounds showed very potent antitumour activity, especially analogues **12** (IC_{50} 0.02 μM against MDA-MB 231 cells) and **14** (IC_{50} 0.21 μM against HeLa cells), which displayed the highest activity of all compounds under evaluation. A brief SAR study points to the structural features that are beneficial for antiproliferative activity of synthesized 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. This represents a possible clue for the development of a variety of new anticancer agents bearing an α,β-unsaturated δ-lactone scaffold and modified aromatic moieties. This will be the subject of our future studies.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures, full characterization data, and copies of NMR spectra of final products) associated with this article can be found, in the online version. These data include MOL files and InChiKeys of the most important compounds described in this article.

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Graphical Abstract

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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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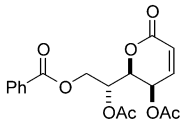
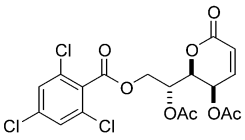
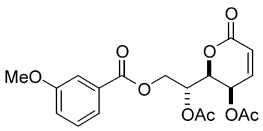


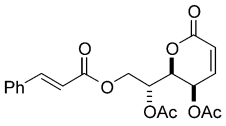
(–)-cleistenolide (**1**)
IC_{50} 1.21 μM (HL-60)



12
IC_{50} 0.02 μM (MDA-MB 231)



13
IC_{50} 0.89 μM (HL-60)



14
IC_{50} 0.21 μM (HeLa)