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Synthesis and Cytotoxicity of Semisynthetic Withalongolide A Analogues

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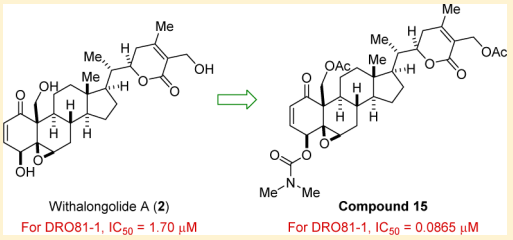
Supporting Information

ABSTRACT: The natural product withaferin A exhibits potent antitumor activity and other diverse pharmacological activities. The recently discovered withalongolide A, a C-19 hydroxylated congener of withaferin A, was recently reported to possess cytotoxic activity against head and neck squamous cell carcinomas. Semisynthetic acetylated analogues of withalongolide A were shown to be considerably more cytotoxic than the parent compound. To further explore the structure−activity relationships, 20 new semisynthetic analogues of withalongolide A were synthesized and evaluated for cytotoxic activity against four different cancer cell lines. A number of derivatives were found to be more potent than the parent compound and withaferin A.



KEYWORDS: *Withalongolide A, withaferin A, triacetate, jaborosalactone, macrocycle, DRO81-1*

Withanolides are a group of naturally occurring C28 steroidal lactones assembled on an ergostane skeleton. Most of the withanolides are highly oxygenated members of the Solanaceae family.[1,2] Withaferin A (**1**; Figure 1) has a wide range of biological activities, such as antitumor, antimicrobial, antioxidant, anti-inflammatory, immunomodulatory, protective, and antiangiogenic effects.[1−6] The antitumor activity of withaferin A results from targeting multiple signaling pathways such as HSP90 and NF-κB that may circumvent the development of resistance among cancer cells.[7−11]

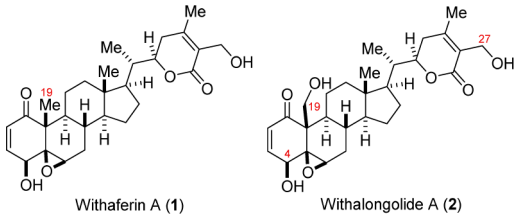


Figure 1. Chemical structures of withaferin A and its C-19 oxygenated analogue, withalongolide A.

Recently, Zhang et al. reported the isolation, structures, and cytotoxic activities of withanolides featuring the presence of a rare C-19 hydroxy group.[12,13] Withalongolide A (**2**; Figure 1) was found to be less potent than withaferin A against the carcinoma and melanoma cell lines tested. However, the semisynthetic derivatives withalongolide A 4,27-diacetate **7** and withalongolide A 4,19,27-triacetate **8** (Scheme 1) showed improved potency and selectivity against the melanoma cell line B16F10 over both the parent compounds **2** and **1**.[12] This led us to initiate a study to examine preliminary structure−activity relationships (SARs) for compound **2**. In this letter, we report the synthesis and biological evaluation of 20 new semisynthetic analogues of this fascinating class of cytotoxic agents.

Previous authors have asserted that a 2-ene-1-one, a 5β,6β-epoxide, and a 17β-oriented δ-lactone are essential for biological activity.[2,14,15] Accordingly, we initially sought to minimize modifications at these positions. Moreover, since the di- and triacetate of compound **2** displayed significant selectivity against melanoma cell line B16F10 with a potency in nanomolar range, we first focused on examining the effects of different derivatives of the free hydroxyl group of **2**.

Accordingly, we prepared a series of aliphatic esters of **2** (Scheme 1). After slight modifications of the standard acetylation procedures, it was possible to isolate mono- (**3**−**5**) and diacetylated analogues **6** and **7**[12] from the same reaction along with some recovered **2** (acetic anhydride was added in two portions; see the Supporting Information for details). Withalongolide A 4,19,27-triacetate **8**[12] and withalongolide A

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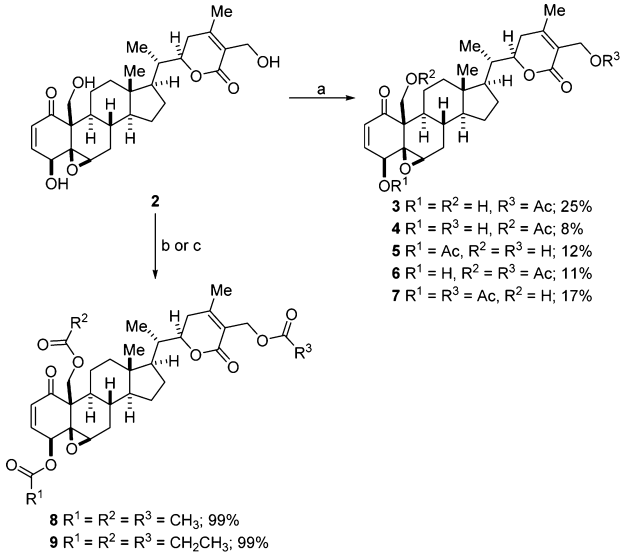
Scheme 1. Synthesis of Acetylated and Propionylated Analogues of Withalongolide A (2)[a]



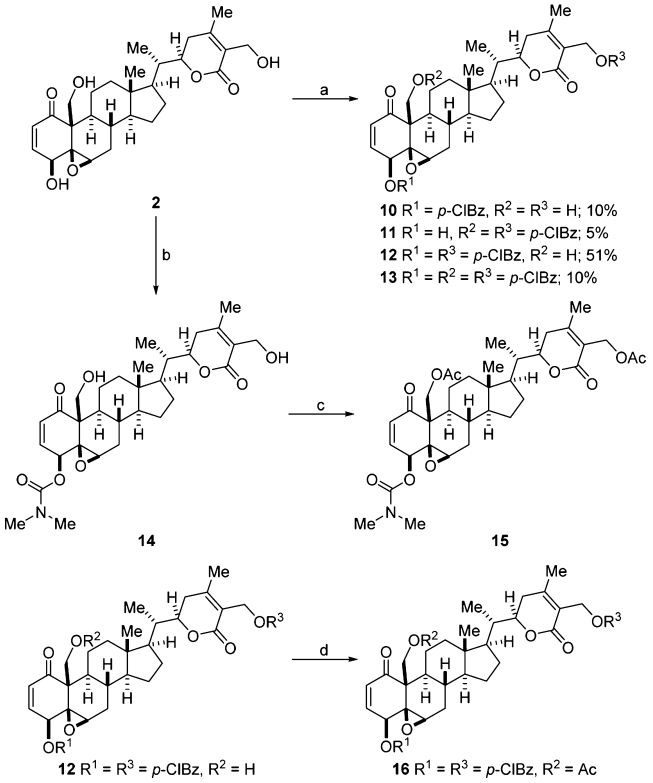
[a]Reagents and conditions: (a) For **3**–**7**, $(CH_3CO)_2O$, pyridine, rt, 73% combined yield; (b) for **8**, $(CH_3CO)_2O$, pyridine, DMAP, rt, 99%; (c) for **9**, $(CH_3CH_2CO)_2O$, pyridine, DMAP, rt, 99%.

4,19,27-propionate **9** were obtained by treating **2** with appropriate anhydrides in the presence of pyridine and a catalytic amount of 4-(dimethylamino)pyridine (DMAP).

The second series of analogues entailed the synthesis of acetates and aromatic esters in assorted combinations along with carbamates (Scheme 2). The reaction of **2** with *p*-chlorobenzoyl chloride under typical acylation conditions afforded a mixture from which mono- (**10**), di- (**11** and **12**), and tri-*p*-chlorobenzoate ester **13** were isolated.[16] The free C-19 hydroxyl group of **12** was further acetylated with acetic anhydride to afford compound **16**. Carbamoylation only occurred at the C-4 hydroxyl, even after treating **2** with excess dimethylcarbamoyl chloride, to afford monosubstituted dimethylcarbamate analogue **14**. Subsequent acetylation of the remaining two hydroxyl groups with acetic anhydride delivered compound **15** in good yield. Efforts to make carbonate analogues from phenylchloroformate led to a multitude of products, which seemed to be unstable.

Jaborosalactones are withanolides isolated from *Jaborosa* species. We synthetically prepared close derivatives of known jaborosalactones by chemically manipulating **8** as shown in Scheme 3. Thus, the palladium-catalyzed, formate-mediated reduction of triacetate **8** afforded a mixture of jaborosalactone derivatives **17**[17] and **18**[18,19] through C-4 deoxygenation of the acetate group.[20] The structure of the diacetate analogue of jaborosalactone V **17** was confirmed by single-crystal X-ray diffraction analysis (Figure 2).[17] Compound **18**, a C-19 acetate analogue of jaborosalactone B 27-acetate was obtained via similar C-4 deoxygenation followed by subsequent epoxide ring-opening.[18,19] Analogue **19**, a C-19 acetate derivative of jaborosalactone E 27-acetate, was obtained by epoxide ring-opening of compound **17** using hydrogen chloride solution in ether.[21] Besides being expected from a mechanistic perspective, antirelationship of the C-5 chlorine and C-6 hydroxyl groups was assigned based on NMR data comparison with the literature values for jaborosalactone E and similar compounds.[22,23] Acetylation of a small amount of compound **19**

Scheme 2. Synthesis of Benzoylated and Carbamate Analogues of Withalongolide A (2)[a]



[a]Reagents and conditions: (a) For **10**–**13**, *p*-chlorobenzoyl chloride, triethylamine, DMAP, CH_2Cl_2, rt, 76% combined yield; (b) $(CH_3)_2NCOCl$, triethylamine, DMAP, CH_2Cl_2, rt, 73%; (c) $(CH_3CO)_2O$, pyridine, DMAP, rt, 70%; (d) $(CH_3CO)_2O$, triethylamine, DMAP, CH_2Cl_2, rt, 95%.

showed a downfield shift of H-6 from δ 3.99 to 5.12 ppm suggesting the presence of a hydroxyl group at C-6 (data not shown).[21,24] The C-6 free hydroxyl group of compound **18** was further acetylated to provide triacetylated analogue **20**.

The α,β-unsaturated ketone of withaferin A is a Michael acceptor.[10] Therefore, we sought to modify the α,β-unsaturated ketone in order to modulate its reactivity. Initial attempts to perform Diels–Alder reactions on the $\Delta^{2,3}$-olefin were unsuccessful. Subsequent efforts were directed toward the synthesis of α-substituted aryl analogues of the ring A enone of **2**. Compound **2** and its triacetate analogue **8** were subjected to α-iodination conditions using iodine and DMAP to afford their corresponding α-iodoenone analogues **21** and **22** (Scheme 4).[25] However, attempts to modify these α-iodoenones through Suzuki cross-coupling with boronic acids[26,27] to obtain α-aryl analogues met with no success; only decomposition of the α-iodoenones was observed.

The final analogue was prepared via ring-closing macrocyclization[28,29] to afford a rare steroidal macrocycle (Scheme 5).[30,31] Thus, bis-acylation of withalongolide monoacetate **3** with 4-pentenoic anhydride afforded **23**. Ring-closing metathesis with Grubb's II catalyst exclusively afforded the 14-membered macrocycle **24** with *E*-configuration.[32]

All synthesized analogues of **2**, along with withaferin A as a positive control, were tested for their cytotoxic activity against four cancer cell lines: head and neck squamous cell carcinoma (HNSCC, JMAR), breast cancer cells (MDA-MB-231),

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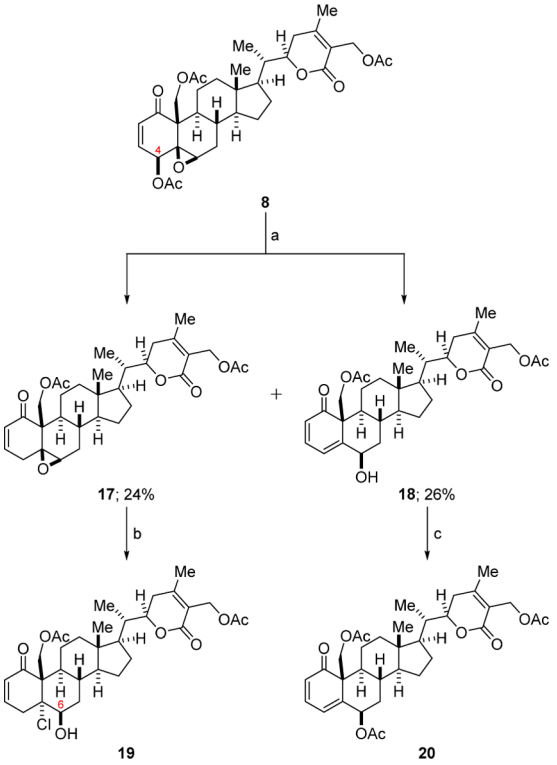
Scheme 3. Synthesis of Jaborosalactone Derivatives from Triacetate 8[a]



[a]Reagents and conditions: (a) $Pd(OAc)_2$, PPh_3, HCO_2NH_4, dioxane, reflux, 50% combined yield; (b) HCl solution in ether, CH_2Cl_2, rt, 70%; (c) $(CH_3CO)_2O$, pyridine, DMAP, rt, 87%.

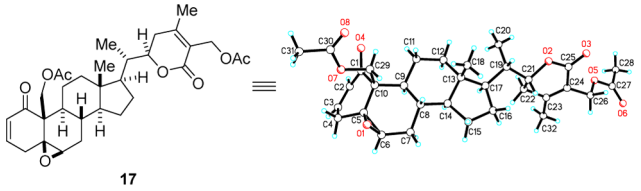
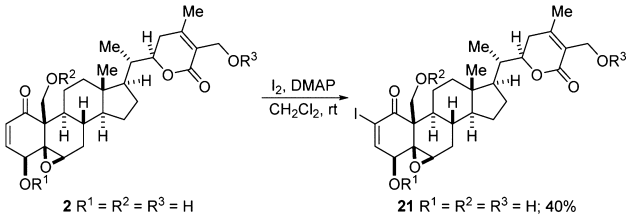


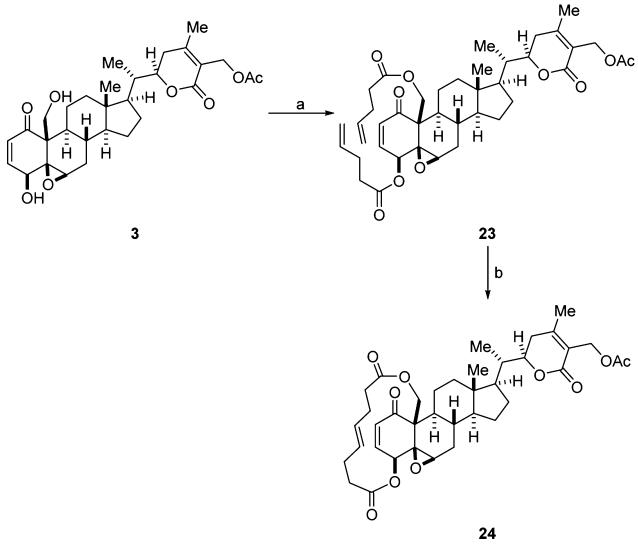
Figure 2. Single-crystal X-ray structure of analogue **17**.

Scheme 4. Synthesis of α-Iodoenone Derivatives



melanoma (SKMEL-28), and colon cancer cells (DRO81-1), in addition to normal fetal lung fibroblast (MRC-5) cells (Table 1). Compound **2** was less potent than withaferin A, as previously reported.[12] Acetylation of compound **2** resulted in more potent analogues with diacetates (**6** and **7**) and triacetate **8** exhibiting enhanced cytotoxic activity than the monoacetylated analogues (**3**, **4**, and **5**). Notably, compound **7** was found to be selectively cytotoxic toward DRO81-1 with an IC_{50} value of 0.0580 μM.[12] The tripropionylated analogue **9** was also active with IC_{50} values in the range of 0.130−1.00 μM. The

Scheme 5. Synthesis of Steroidal Macrocycle 24 from Withalongolide Monoacetate 3[a]



[a]Reagents and conditions: (a) $(H_2C{=}CHCH_2CH_2CO)_2O$, pyridine, DMAP, rt, 92%; (b) Grubb's II catalyst, CH_2Cl_2, 37 °C, 87%.

Table 1. Cytotoxicity Activity (IC_{50} Values in μM) of Withalongolide A Analogues against Five Cell Lines[a]

compd	JMAR	MDA-MB-231	SKMEL-28	DRO81-1	MRC-5
1	1.00	0.540	1.00	0.780	2.70
2	3.10	1.50	1.60	1.70	5.30
3	1.22	0.415	0.705	1.05	2.30
4	3.06	1.15	1.23	0.780	1.80
5	2.48	0.890	1.22	0.570	1.20
6	0.515	0.205	0.230	0.155	0.490
7	0.600	0.635	0.170	**0.0580**	0.295
8	0.655	0.655	0.110	0.110	0.310
9	1.00	0.365	0.285	0.130	0.615
10	1.72	1.40	2.25	1.85	2.55
11	4.64	2.62	1.11	1.90	2.35
12	>10	>10	>10	>10	>10
13	>10	>10	>10	>10	>10
14	2.09	0.610	0.515	0.585	1.75
15	0.970	0.175	0.205	**0.0865**	0.510
16	>10	>10	>10	>10	>10
17	1.22	0.790	0.710	1.10	2.05
18	>10	>10	>10	>10	>10
19	2.16	0.800	1.17	1.35	3.15
20	>10	>10	>10	>10	>10
21	>10	>10	9.11	5.25	9.10
22	0.830	0.210	0.275	0.115	0.475
23	1.44	0.625	0.470	0.580	0.865
24	0.965	0.245	0.205	0.225	0.360

[a]Analogues **12**, **13**, **16**, **18**, and **20** were inactive with $IC_{50} \geq 10$ μM for all cell lines tested.

increased cytotoxic potency of the di- and triacetate analogues of **2** could be due to increased lipophilicity leading to enhanced cell permeability.[16,33,34]

Although the mono-*p*-chlorobenzoylated derivative **10** and C-19,27-dibenzoylated analogue **11** were active, the C-4,27-dibenzoylated analogue **12** and tribenzoylated compound **13** were not. Compounds **14** and **15** exhibited higher cytotoxic activity than **2**, with compound **15** displaying 3−5 times

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increased cytotoxicity against breast cancer and melanoma cells compared to **1**. Compound **15** also demonstrated modest selectivity toward DRO81-1 cells with an IC_{50} value of 0.0865 μM, similar to compound **7**.

Jaborosalactone V diacetate **17** was found to be equipotent to withaferin A **1**, suggesting that C-4 hydroxyl group is not crucial for activity.[2,15] Compound **19**, containing a 5α,6β-chlorohydrin, was slightly less potent than the 5β,6β-epoxy analogue **17**, with IC_{50} values in the range of 0.800−2.16 μM against melanoma and carcinoma cells. The cytotoxic activity was abolished in epoxide-lacking analogues **18** and **20**.[2,15]

Even though the 2-iodoenone analogue **22** displayed comparable cytotoxicity to its parent compound **8**, compound **21** showed very weak activity compared to **2**. Interestingly, macrocycle **24** exhibited increased potency compared to its acyclic analogue **23** across all cell lines tested with IC_{50} values in the range of 0.205−0.965 μM.[28,29] Most of the active analogues were moderately selective toward cancer cells compared to normal fibroblast cells.

In our efforts to contribute toward the development of anticancer-related therapeutics, we have identified additional cytotoxic agents based on the natural product withalongolide A **2**. Many of these analogues were more potent than the parent compound, and the SAR profile was in good agreement with those previously reported for withanolides having similar structures.[1,2,15,16] The selectivity of analogues **7** and **15** toward colon cancer cells (DRO81-1) is intriguing, and further efforts are underway to study these analogues as potential anticancer agents.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, cytotoxicity assay, details of the crystal structure of compound **17**, characterization data, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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