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Synthesis and antifungal activity of functionalized 2,3-spirostane isomers

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ABSTRACT

Invasive fungal infections are a major complication for individuals with compromised immune systems. One of the most significant challenges in the treatment of invasive fungal infections is the increased resistance of many organisms to widely used antifungals, making the development of novel antifungal agents essential. Many naturally occurring products have been found to be effective antimicrobial agents. In particular, saponins with spirostane glycosidic moieties—isolated from plant or marine species—have been shown to possess a range of antimicrobial properties. In this report, we outline a novel approach to the synthesis of a number of functionalized spirostane molecules that can be further used as building blocks for novel spirostane-linked glycosides and present results from the in vitro screenings of the antifungal potential of each derivative against four fungal species, including *Candida albicans*, *Cryptococcus neoformans*, *Candida glabrata*, and the filamentous fungus *Aspergillus fumigatus*.

Invasive fungal infections are a major complication for individuals subjected to bone marrow transplants, neutropenic cancer patients, and in individuals suffering from HIV and AIDS.[1,2] Reports indicate that mortality rates attributed to fungal infections in immuno-compromised individuals can range between 30% and 70%,[3] depending on the time of detection of the infection. Adding to current challenges in treating immune-compromised individuals are filamentous fungi, such as *Aspergillus* and *Scedosporium*, which can infect the respiratory tract or lead to disseminated blood stream infections, respectively.[4–9] Both are exceptionally difficult to treat with common antifungals; additionally, a growing number of organisms are becoming more threatening to the patient population due to increased drug resistance.[10–12] Considering these facts, the design and synthesis of novel antifungal agents remains an area of intense significance.

Over the last few decades, many naturally occurring products have been described as effective antimicrobial agents.[13–16] Among these natural products are saponins, many of which are steroidal glycosides isolated from plant or marine species.[14] Several saponins have been described as having potent antimicrobial properties.[2,17,18] Furthermore, a number of saponins with either a spirostanol or a 2,3-spirostandiol moiety linked to a glycoside exhibit broad spectrum antifungal activity against multiple fungal species,[17,19,20] where the mechanism of action is probably through the formation of a complex with sterols in fungal membranes causing a loss of membrane integrity[21] or by inhibiting 1,3-β glucan synthase activity.[22,23] Therefore, it is reasonable to investigate the development of novel 2,3-spirostane based glycosides as potential antifungal agents. Nonetheless, while there are reports showing successful syntheses of spirostanols,[24–26] a major obstacle remains in the limited synthetic methodology applicable to large-scale preparations of functionalized 2,3-spirostanes. Developing this synthetic methodology would not only allow the preliminary investigation of functionalized 2,3-spirostanes as potential antifungal agents but would also provide a library of functionalized 2,3-spirostane derivatives that could be used as building blocks for the development of novel synthetic spirostane-linked glycosides with potential antimicrobial properties. To this end, in this report we outline novel approaches to the synthesis of functionalized 2,3-spirostane isomers and present results from preliminary in vitro screenings of the antifungal activities of each derivative against four fungal species, including *Candida albicans*, *Cryptococcus neoformans*, *Candida glabrata*, and the filamentous fungus *Aspergillus fumigatus*.

Functionalized steroids are well known compounds with potentially interesting biological properties.[27–29] Many of these compounds are only available in milligram quantities, as they are isolated from natural sources. This limited availability hampers both chemical and biological exploration of these compounds and their analogs. Therefore, there is an urgency to develop well-defined synthetic procedures for the preparation of these valuable compounds in large quantities starting with inexpensive and commercially available steroid precursors. To this end, we selected

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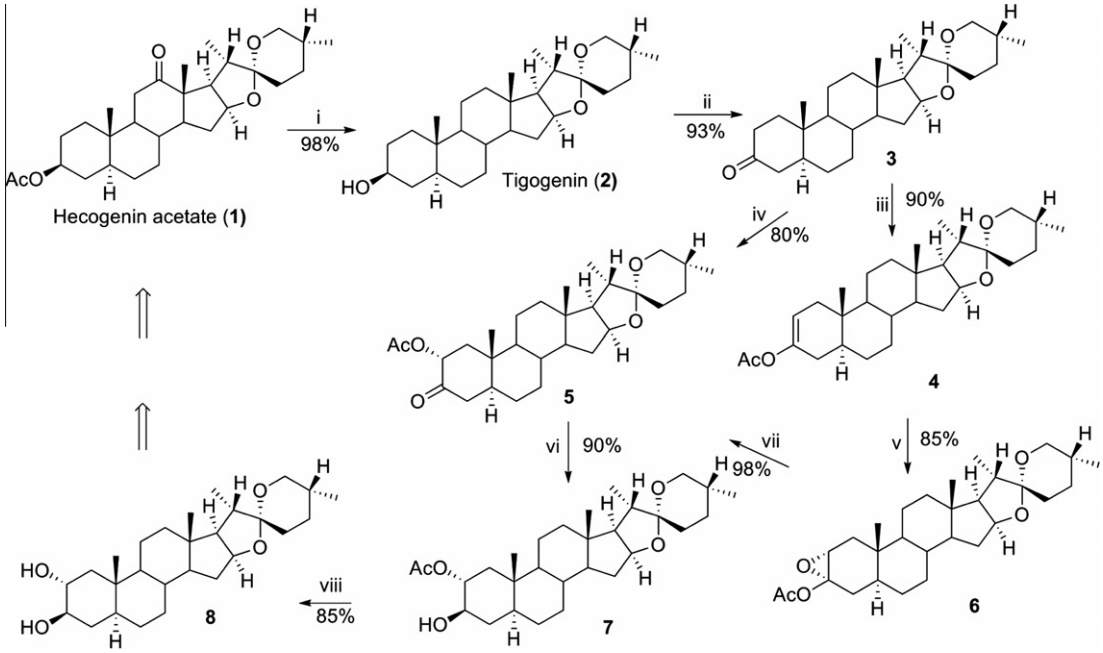
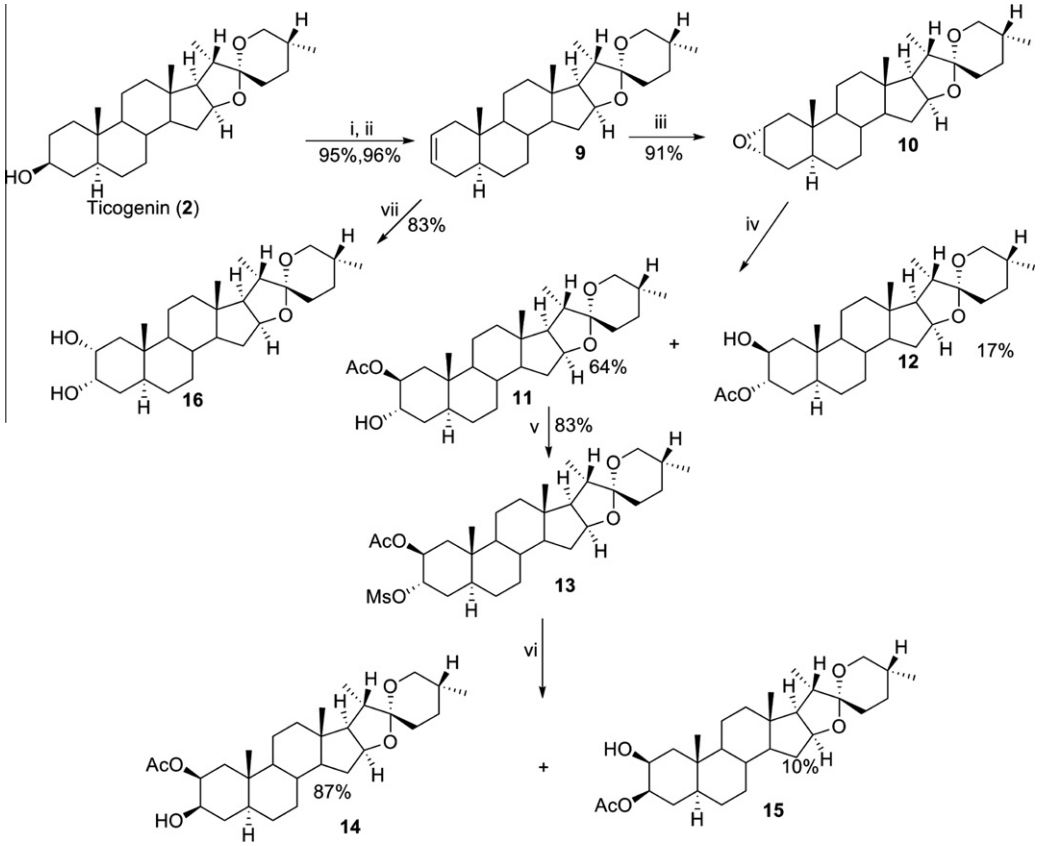
hecogenin acetate ((**1**) Scheme 1) as the starting material for the development of our spirostane building blocks. Our overarching goal was to develop an efficient synthetic procedure for the synthesis and isolation of functionalized 2,3-spirostanes that could be further used to develop novel saponin-like analogs with potential therapeutic value.



Scheme 1. Synthetic steps in preparation of 5α-spirostan-2α,3β-diol (**8**) from hecogenin acetate (**1**). Reagents and conditions: (i) hydrazine hydrate, 2-ethoxyethanol, KOH, 136 °C; (ii) CrO_3/H_2SO_4/dry acetone; (iii) $(CH_3CO)_2CO$/Montmorillonite clay; (iv) $Pb(O_2CCH_3)_4/(CH_3CO)_2O–CH_3CO_2H$; (v) *m*-chloroperbenzoic acid/CH_2Cl_2; (vi) $CeCl_2{\cdot}7H_2O/CH_3OH$/tetrahydrofuran/$NaBH_4$; (vii) $(CH_3CO)_2/N(C_2H_5)_3$; (viii) $NaOH/CH_2Cl_2/CH_3OH$.



Scheme 2. Preparation of alpha mono acetates of spirostanes. Reagents and conditions: (i) NaH/CS_2/propargyl bromide/THF; (ii) collidinium trifluoromethanesulfonate (0.1 equiv)/toluene/reflux; (iii) *m*-chloroperbenzoic acid/CH_2Cl_2; (iv) acetic acid/reflux; (v) $MsCl/Et_3N/CH_2Cl_2$; (vi) pyridine/water/reflux; (vii) OsO_4/*N*-methylmorpholine-*N*-oxide.

We explored a number of different synthetic pathways in the preparation of functionalized 2,3-spirostanes. Here we are presenting the two most efficient routes, each of which was superior to our alternative synthetic routes in simplicity, isolated yields, and applicability to the preparation of other substituted steroids in large quantities. The preparation of our functionalized 2,3-spirostanes started with the one-pot simultaneous ester group hydrolysis and Wolff–Kishner keto group reduction of hecogenin acetate ((**1**) Scheme 1).[30] This procedure was adapted from a well developed method for the preparation of tigogenin ((**2**) Scheme 1) from hecogenin.[31] Using this approach, we produced a large quantity of tigogenin (**2**) in excess of 98% yield, which was then used for further chemical modification to produce alternative stereoisomers.

In designing the synthetic methodology to prepare functionalized 2,3-spirostane stereoisomers, we identified two major obstacles that required resolution prior to the development of a practical synthetic approach. The first was (a) how to selectively introduce hydroxyl groups into the C-2 position; and the second was (b) how to differentiate one of the two hydroxyl groups for hydroxyl group protection in order to modify the other synthetically. For 5α-spirostan-2α,3β-diol ((**8**) Scheme 1), this was elegantly accomplished with three highly efficient synthetic steps (Scheme 1, steps ii, iv and vi). In the first step, a Jones oxidation of the OH group in the 3 position of tigogenin (**2**) was used to prepare ketone (**3**) (Scheme 1).[32] This oxidation was necessary because it allows for an acetoxy group to be introduced into the α-position to the carbonyl.[33] Typically, this reaction produces several acetoxy isomers, but in the case of steroid substitution, the reaction is both highly site and stereospecific. The acetoxy group is introduced in the C-2 position rather than in C-4 position due to steric hindrance of C-4 steroids. Further, the reaction occurs from the α-face of steroid, due to β-face steric hindrance, and therefore the only isolated product is the keto ester **5** (Scheme 1). The preference for α-face substitutions in steroid reactions has been well documented.[34,35] We further used this knowledge to perform the stereoselective sodium borohydride reduction of keto ester **5**, a reaction that produced only the 3β-hydroxy isomer **7** in 90% isolated yield (Scheme 1). Finally, to complete our synthetic route

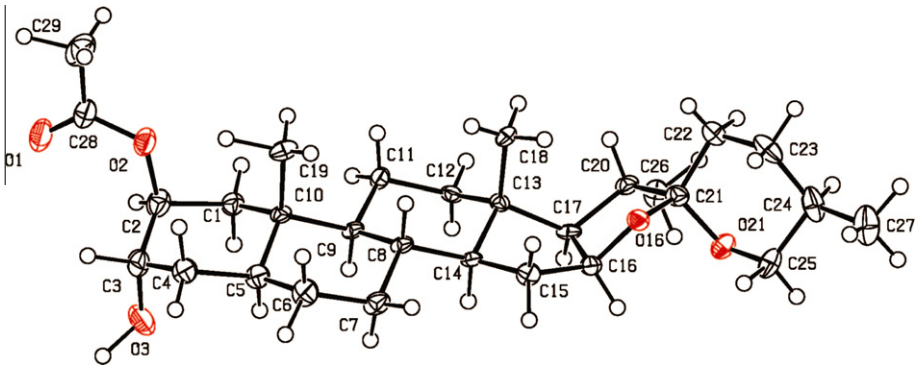
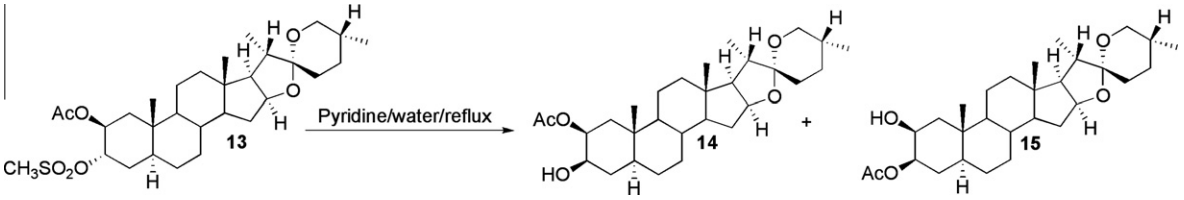
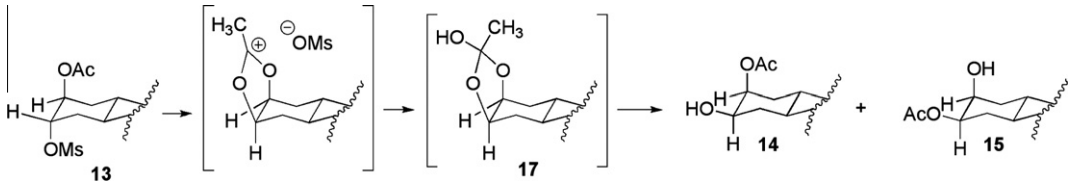


Figure 1. The ORTEP drawing of X-ray determined structure of **11**. CCDC deposition number 817921.

Table 1
Inversion of the C-3 mesylate of **13** to form **14** and **15**

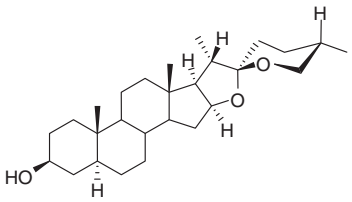
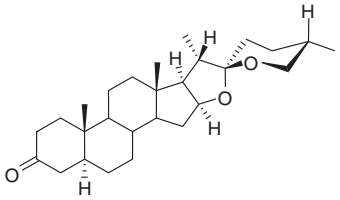
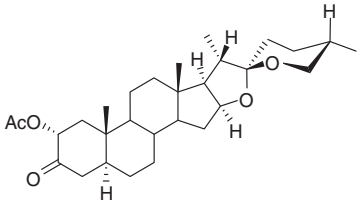
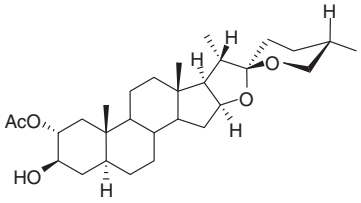
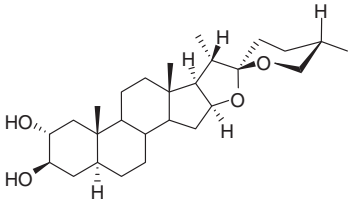
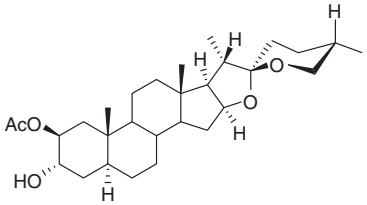
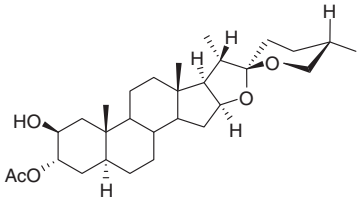
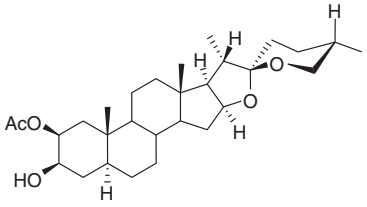


Solvent	*T* (°C)	Time (h)	Conversion (%)	Ratio **14**:**15**
Toluene (dry)	100	48	70	1:1
Toluene (wet)	100	48	80	1:1
Toluene with $Bu_4N^+NO_3^-$	110	2	20	1:9
Toluene with $Bu_4N^+NO_3$	110	20	100	4:6
5% water in acetone	56	24	20	1:9
5% water in pyridine	100	7	100	1:9



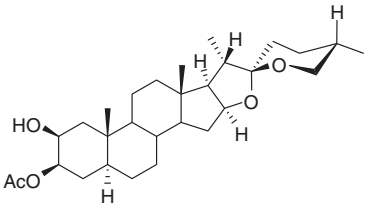
Scheme 3. Proposed mechanism for acetyl group assisted hydrolysis of mesylate **13**.

Table 2
Antifungal activities of novel spirostane analogs (MIC in μg/mL)

Compound	Structure	MIC_{50}[a,f] (μg/mL)			
		C. albicans [b]	*C. glabrata*[c]	*C. neoformans*[d]	*A. fumigatus*[e]
2		NC*	>62.5	NC*	16
3		NC*	NC*	NC*	NC*
5		32	NC*	NC*	>128
7		16	6.25	62.5	>128
8		NC*	NC*	NC*	NC*
11		NC*	NC*	NC*	NC*
12		NC*	NC*	NC*	NC*
14		NC*	NC*	NC*	NC*

(*continued on next page*)

Table 2 (*continued*)

Compound	Structure	MIC$_{50}$[a,f] (μg/mL)			
		C. albicans [b]	*C. glabrata*[c]	*C. neoformans*[d]	*A. fumigatus*[e]
15		NC*	NC*	NC*	NC*

[a] MIC values are reported only for compounds displaying (1) a prominent decrease in turbidity by visual comparison to the control wells containing no antifungal and (2) a >50% reduction in fungal growth compared to controls containing no antifungal, as measured spectroscopically by absorption at 530 nm.
[b] ATCC No. 10231.
[c] ATCC No. 48435.
[d] ATCC No. 36556.
[e] ATCC No. 16424.
[f] All values were determined after incubation at 35 °C for 48 h.
* Denotes compounds that had (1) a slight reduction in turbidity to no change and (2) had less than a 25% reduction in growth compared to controls, as measured spectroscopically by absorption at 530 nm.

toward the preparation of 5α-spirostan-2α,3β-diol ((**8**) Scheme 1) the ester group of **7** was hydrolyzed in NaOH/methanol + dichloromethane to yield compound **8**.

Alternatively, we also developed a highly efficient alternative synthetic approach for the preparation of keto acetate **5** (Scheme 1), avoiding the use of lead tetraacetate, due to pharmacological controversy surrounding this reagent.[36] In our alternative approach, we replaced the lead tetraacetate step (Scheme 1, step iv) with three very simple and efficient synthetic steps: (a) the transfer of ketone **3** into its vinyl acetate **4** (Scheme 1, step iii), (b) the MCPBA epoxidation of vinyl acetate **4** into epoxide **6** (Scheme 1, step v), and finally; (c) the acetic acid epoxide **6** ring opening (step vii, Scheme 1). This three step combination that replaced lead tetraacetate with less controversial reagents did ultimately give a slightly lower overall yield (75%) for compound **5** than what is isolated from a direct reaction with lead tetraacetate (80%), however it can still be used as a safe alternative for the preparation of intermediate **5** in our synthesis of functionalized 2,3-spirostanes.

After accomplishing the synthesis of 5α-spirostan-2α,3β-diol (**8**) we focused on the synthetic preparation of its stereoisomers (Scheme 2). As mentioned previously, it is well documented that the α-steroid face is less sterically hindered and therefore is the more reactive face of the steroid. This selective reactivity was used to prepare the axial *trans* dihydroxy derivatives **11** and **12** (Scheme 2). The synthesis started with a modified Chugaiev water elimination[37] from tigogenin **2** (Scheme 2). As in many other cases, epoxidation of 2-spirostene ((**9**) Scheme 2) occurred from the α-face[38,39] and generated epoxide **10** (Scheme 2). The acetic acid epoxide ring opening resulted in the axial hydroxyl acetate **11** and **12** (Scheme 2). The structure of **11** was also confirmed by X-ray crystallography (Fig. 1).

In addition to producing functionalized isomers **11** and **12**, we also generated synthetically the α-*cis*-diols from compound **9**. This was accomplished by using an established procedure involving OsO4 oxidation of unsaturated steroids, such as **9** (Scheme 2).[40] Using this method, 5α-spirostan-2α,3α-diol (**16**) was prepared in 83% isolated yield.

Of the isomers prepared, the more demanding was 5α-spirostan-2β,3β-diol. Considering that the preparation of acetyl **11** (Scheme 2) was a straightforward process, we decided to use this compound as a starting point to explore its C-3 stereochemical inversion. Inversion through acetyl group rearrangement is a well known reaction.[41] We used this approach to explore the effect of acetyl neighboring group participation on the hydrolysis of mesylate **13** (Scheme 2). Various reaction conditions were explored (Table 1). In toluene as a reaction medium, an equimolar ratio of esters **14** and **15** can be obtained, but if the reaction is carried out in wet pyridine, predominantly ester **14** is prepared (as determined by integral ratios from ^{1}H NMR and from isolated yields of products where 87% isolated yield was obtained from **14** and 10% isolated yield was obtained from **15**). This can be explained only by the formation of the tetrahedral intermediate (**17**, Scheme 3). The proposed structural intermediate shown in Scheme 3 is based on the fact that acetyl groups remain on the β-face of the steroid (**14** and **15**) and there is no formation of the two α-hydroxy isomers. The structure assignments of **14** and **15** were made by comparing the NMRs of these two compounds to the NMRs of tigogenin (**2**) and compound **11**, both of which have well establish structures. The shape and chemical shifts of 2α and 3α hydrogens vary if hydroxy or acetoxy groups are in their geminal position. The 2α hydrogen is a multiplet (two overlapping triplets) with a chemical shift ~4.8 ppm for the geminal hydroxyl group and it is a singlet with a chemical shift ~5.0 ppm for the acetoxy group. On the other hand, the 3α hydrogen in both cases is a quartet (two overlapping triplets) with a chemical shift around ~4.4 ppm for both geminal hydroxy and acetoxy groups. Compound **14** has singlet at 5.14 ppm (geminal acetoxy) and a quartet at 4.39 ppm (geminal hydroxyl), while compound **15** has a multiplet at 4.78 ppm (geminal hydroxyl) and a quartet at 4.39 ppm (germinal acetoxy). This is consistent with chemical shifts and signal shapes for **2** and **11**.

The antifungal activity of the synthesized functionalized 2,3-spirostanes were evaluated in vitro using four species of fungi, including *C. albicans*, *C. neoformans*, *C. glabrata*, and the filamentous fungus *A. fumigatus*. The results of these screenings are summarized in Table 2. Of the nine analogs tested, 2α-acetoxy-5α-spirostan-3β-ol (**7**) was the only compound that showed significant antifungal activity (>50% inhibition at the minimal concentration) against all four species tested, with *C. glabrata* being the most sensitive at the lowest concentration (6.25 μg/mL) and the filamentous fungi *A. fumigatus* being the least sensitive (where 50% inhibition was only observed in the highest dose tested—128 μg/mL). Hydrolysis of the acetoxy group of **7** (yielding compound **8**) resulted in the total loss of antifungal activity against all species tested, as did inversion of the stereocenter on the C-3 (to yield compound **14**) as well as on the C-2 and C-3 positions (to yield compound **11**) of isomer **7** (Table 2). The combination of the change in stereochemistry of both the chiral C-2 and C-3 centers

and the acetyl group migration from C-2 to C-3 of **7** resulted in the total loss of antifungal activity (see **12**, Table 2). Finally, the inversion of only one of the chiral centers of **7** (C-2 inversion to yield **15**, Table 2) resulted in the total loss of antifungal activity.

In addition to analyzing in vitro the antifungal properties of all acetate ester and free 2,3-spirostane isomers, we also analyzed three intermediate compounds with structural similarities to compound **7**. These analogs included compounds **2** (tigogenin), **3** and **5** (Table 2). Interestingly, the analog tigogenin (**2**), which contains a β-face OH group in the C-3 position, similar to **7**, displayed significantly increased activity against *C. glabrata* and *A. fumigatus* (>62 and 16 μg/mL, respectively) compared to **7** (Table 2). One can speculate this might be due to the orientation of the binding sites to which these compounds may be binding. Further studies with analogs that contain various sugar and hydrocarbon substitutions to both the α- and β-faces of the spirostane molecule are currently underway. Nonetheless, the preliminary antifungal evaluation of 2,3-functionalized spirostanes identified several of the derivatives that showed moderate antifungal activity (as measured spectroscopically by a >50% reduction in fungal growth compared to control wells), against at least one species of fungus. These 2,3-functionalized derivatives will be used as building blocks for the synthesis of novel spirostane-linked glycosides.

Detailed information regarding the syntheses, spectroscopic characterization and biological evaluation of the functionalized 2,3-spirostanes presented in this Letter can be found in the Supplementary data provided. X-ray coordinates were deposited in CCDC database (CCDC number 817921).

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2011.03.092.

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