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Antifungal Sordarins. Synthesis and Structure–Activity Relationships of 3′,4′-Fused Dioxolane and Dioxane Derivatives

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Abstract—A number of novel 3′,4′-fused dioxolane and dioxane sordarin derivatives were synthesised for structure–activity relationship studies. Many of these derivatives exhibit high activity against *Candida* spp. and *Cryptococcus neoformans*.

Systemic fungal diseases are of growing concern due to the increasing number of immunocompromised patients (cancer, transplants, premature infants, ITU patients, AIDS, etc.). Treatments for these fungal infections are far from satisfactory and restricted to few classes of agents.[1a,b] Polyenes have toxic side effects and limitations in their ways of administration. Azole therapy is threatened by emergence of drug resistance and some azoles have a limited spectrum of action. Echinocandins are only available in intravenous (iv) formulations. Therefore, the development of new drugs with novel modes of action for treating fungal infections continues to be a major challenge.

Sordarins[1c,d] are a new class of antifungal agents which are potent and selective inhibitors of fungal protein synthesis. Sordarins bind to EF-2 when this elongation factor is complexed with the ribosome. A ribosomal stalk protein, P0, is also involved in binding since its mutations lead to resistance to sordarins. Compound **1a** (GR 135402)[2] is a naturally occurring 3′-*O*-acyl derivative of sordarin (**1b**),[3,4] which was discovered in a cell free screening campaign aimed to identify fungal protein synthesis inhibitors. Compound **1a** is also a potent inhibitor of the growth of fungal pathogens like *Candida* spp. and *Cryptococcus neoformans*. In the previous paper we have reported on the preparation of 3′-*O*-acylated and -alkylated sordarins which were found to maintain the antifungal activity of naturally ocurring derivatives with a lipophylic side chain attached to C-3′ position of the sugar ring.[5] We also found that alkylation or acylation of the hydroxy group at 2′ of these derivatives led to a decrease in biological activity. We now report on the effect on the antifungal activity caused by the reduction in conformational flexibility of the pyranose ring with a fused ring attached to C3′–C4′. In this regard, synthetic routes were designed in order to obtain compounds containing fused five- and six-membered rings while maintaining both oxygen atoms at C-3′ and C-4′ present in the sordarin molecule. In addition to this modification, we have studied the role of the hydroxyl group at 2′ position of the pyranose ring by synthesising 2′-deoxy analogues through chemical deoxygenation and changing the 2′-OH stereochemistry in some of the derivatives prepared (Fig. 1).

Chemistry

4′-*O*-Demethylsordarin **2**[6] was the key starting material for the synthesis of these derivatives, its carboxylic acid group was protected as diphenylmethyl (DPM) ester[7] to give compound **3**. Reaction of **3** either with 2,2-

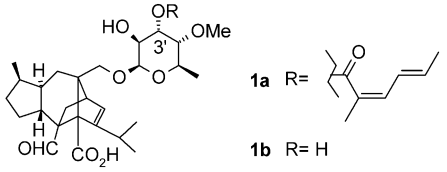

Figure 1. Natural GR 135402 (**1a**) and sordarin (**1b**).

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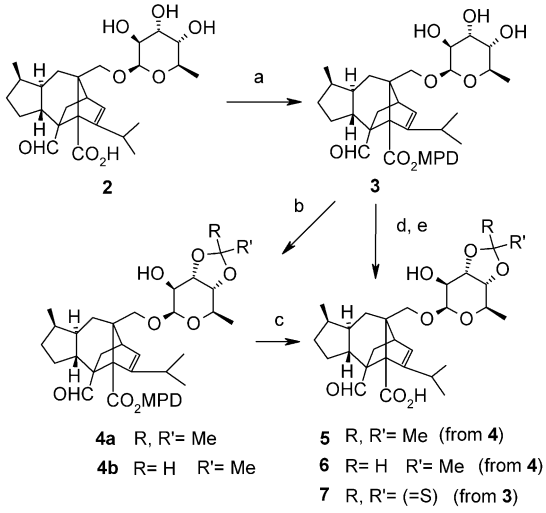
dimethoxypropane or acetaldehyde gave only the regioisomers **4a** and **4b**, respectively, due to the *cis* disposition of the hydroxy groups at 3′ and 4′. Final hydrogenolysis of the diphenylmethyl esters in **4a**–**b** afforded acids **5** and **6** (Scheme 1).[8]



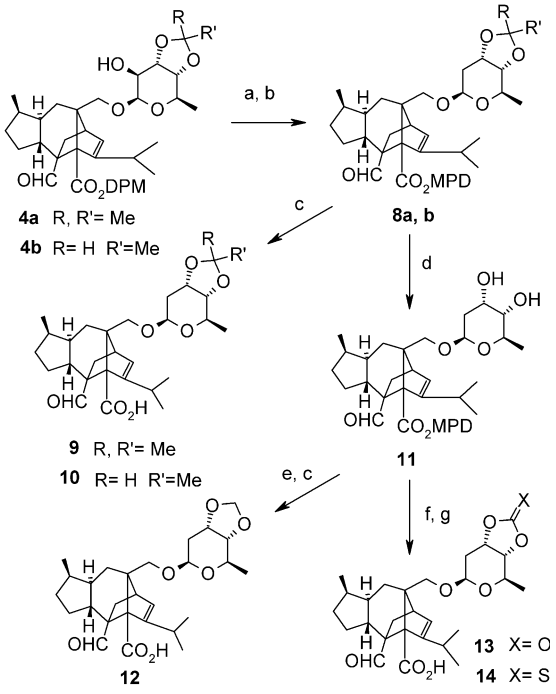
Scheme 1. Reagents and conditions: (a) Ph_2CN_2, CH_2Cl_2 (90%); (b) $Me_2C(MeO)_2$ (or MeCHO), *p*-TsOH, acetone (80–82%); (c) H_2, Pd/C, EtOAc (90–95%); (d) $Im_2C(S)$, toluene, reflux (49%); (e) 5/2 TFA/CH_2Cl_2 (53%).

On the other hand, transformation of intermediate **3** into fused cyclic thiocarbonate **7** was carried out through reaction with 1,1′-thiocarbonyl diimidazole and further acidic diphenylmethyl ester deprotection. In this case, final hydrogenation failed due to catalyst poisoning by sulphur and, therefore, DPM deprotection step was carried out by acidic treatment.

Derivatives lacking the hydroxyl group at position 2′ were obtained following the route depicted in Scheme 2. Intermediates **4a** and **4b** were converted into **8a** and **8b** through 2′-*O*-xanthate via radical deoxygenation.[9] Catalytic hydrogenation afforded acids **9** and **10**. Further transformations of **8a** led to the preparation of other 3′,4′-fused ring derivatives. Thus, the isopropylidene group in **8a** was removed selectively under acidic conditions to afford 3′,4′-diol **11** which served as key intermediate for the preparation of **12**, **13** and **14** (Scheme 2). In this way, reaction of **11** with dibromomethane under phase-transfer conditions[10] yielded unsubstituted dioxolane **12** after final deprotection. Reaction of **11** with 1,1′-carbonyldiimidazole and deprotection afforded cyclic carbonate **13** easily. However, formation of cyclic thiocarbonate analogue **14** needed previous activation of **11** as stannylidene derivative for the acylation reaction with phenyl chlorothioformate.

The 3′,4′-fused dioxane derivative **16** was synthesised from diol **11** using an electrophylic cyclisation methodology (Scheme 3).

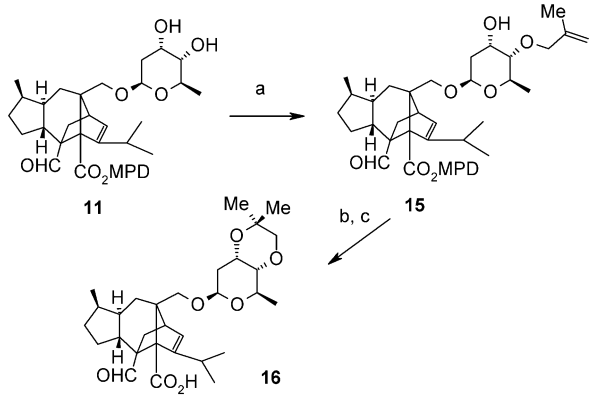
In this way, regioselective alkylation at 4′ to give **15** took place by reaction of **11** with methallyl bromide



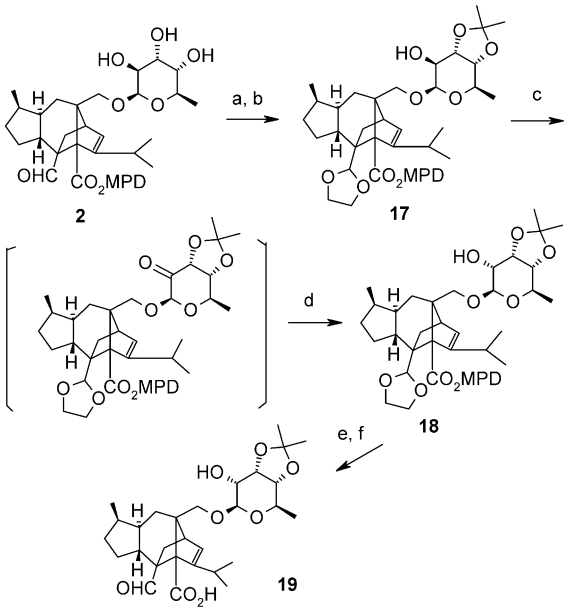
Scheme 2. Reagents and conditions: (a) NaH, imidazole, THF, CS_2; then, MeI (97%); (b) *n*-Bu_3SnH, toluene, reflux (50%); (c) H_2, Pd/C, EtOAc (88%); (d) 1 N HCl, THF–MeOH (78%); (e) Br_2CH_2, TBAB, 50% aq NaOH (44%); (f) for **13**, Im_2CO, CH_2Cl_2 (94%); for **14**, Bu_2SnO, toluene, reflux, ClC(S)OPh (88%); (g) for **13**, H_2, Pd/C, EtOAc (40% for f + g); for **14**, 5/2 TFA/CH_2Cl_2 (79% for f + g).

through the corresponding stannylidene intermediate in fairly good yields. Then, an intramolecular oxymercuriation reaction of **15** was induced by mercuric trifluoroacetate (one equiv) in tetrahydrofuran.[11] In the last step, the mercury atom was removed by reductive homolysis (*n*-Bu_3SnH).[12]

Finally, the 2′-hydroxy epimer **19** was prepared in order to study the influence of the stereochemistry at C-2′ on the antifungal activity (Scheme 4). For this synthesis previous aldehyde protection of **2** (ethyleneglycol, *p*-toluenesulfonic acid) was needed for final selective hydrolysis. A one-step inversion reaction involving oxidation of protected **17** with Collins reagent and subsequent reduction[13] of the 2′-keto derivative



Scheme 3. Reagents and conditions: (a) Bu_2SnO, toluene, reflux; methallyl halide, TBAF, 40 °C (65%); (b) $Hg(CF_3CO_2)_2$, THF, rt; *n*-Bu_3SnH, toluene, reflux (65%); (c) H_2, Pd/C, EtOAc (93%).



Scheme 4. Reagents and conditions: (a) $HO(CH_2)_2OH$, *p*-TsOH, toluene, reflux; (b) $Me_2C(MeO)_2$, *p*-TsOH, acetone (82%); (c) $CrO_3{\cdot}2C_5H_5N$, CH_2Cl_2; (d) $NaBH_4$, MeOH (78% for c + d); (e) H_2, Pd/C, EtOAc; (f) 1 N HCl/MeOH (70% for e + f).

intermediate (sodium borohydride) gave rise to **18**. After carboxyl group deprotection, final selective deprotection of the aldehyde group to **19** was accomplished under acidic conditions.

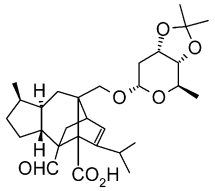
Biological Evaluation

Table 1 shows the in vitro antifungal activity (referred to MIC, the minimum concentration inhibiting fungal cell growth)[14,15] of compounds synthesised. This assay was carried out in broth microdilution using RPMI + -glucose as culture medium.

Results and Discussion

There is an overall increase in potency for those compounds lacking the 2′-hydroxyl group. Thus, 2′-deoxy-3′,4′-isopropylidene derivative **9** is clearly more potent against all the strains of *Candida albicans*, *Candida pseudotropicalis* and *Candida tropicalis* and *C. neoformans* than its 2′-hydroxy analogue **5**. Likewise, a similar correlation can be found with mono-substituted dioxolanes **6** and **10** and the thiocarbonates **7** and **14**. As to the effect of methylidene substitution in dioxolane derivatives, there seems to be a general decrease in antifungal potency when C-3′ and C-4′ oxygen atoms are acylated (carbonate **13** and thiocarbonate **14**) in comparison with isopropylidene **9**, methyldioxolane **10** and dioxolane **12**. When these three derivatives are compared **9** and **10** are 10-fold more potent against *C. albicans* strains than the unsubstituted dioxolane **12**. Whilst this same correlation is valid for activity against *C. pseudotropicalis*, it is reversed for activity against *C. neoformans* (MIC, 0.5 μg/mL for compound **12**). On the other hand, five-membered dioxolane derivatives are considerably more potent than the corresponding six-membered dioxane analogues. Dimethyl-substituted dioxolane **9** is between 10- and a 100-fold more potent against all the *Candida* spp. than the dimethylated dioxane **16**.

Antifungal activity of **19** points out the important effect of the stereochemistry of the hydroxyl group at C-2′. Overall, antifungal potencies of **19** are more than 10-fold lower than those of the corresponding β-analogue **5**. Table 1 also includes compound **20**, the α-anomer of the 2′-deoxy isopropylidene derivative **9**, which has been synthesised separately.[16] Compound **20** is a 1000-fold less potent against *C. albicans* and *C. pseudotropicalis* strains than the analogous β-anomer **9**, indicating the great effect on the antifungal activity caused by the anomeric stereochemistry.



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In conclusion, modification of sordarin pyranose ring by fusing either a dioxolane or a dioxane ring to the

Table 1. Antifungal activity (cell growth inhibitory activity) of synthesised compounds. [MIC (μg/mL)]

Compd	2′ Subst.	3′-4′ Fused	*Candida albicans* 4711E	*Candida albicans* 2005E	*Candida albicans* 2402E	*Candida glabrata* 2375E	*Candida pseudotropicalis* 2371E	*Candida tropicalis* 2808E	*Cryptococcus neoformans* 2867E
5	β-OH	$-OC(Me)_2O-$	0.12	0.12	0.5	31	0.06	1	125
6	β-OH	–OCH(Me)O–	0.5	0.03	—	62	0.5	1	16
7	β-OH	–OC(S)O–	62	31	62	125	31	>125	16
9	H	$-OC(Me)_2O-$	0.004	<0.001	0.008	31	0.004	0.12	8
10	H	–OCH(Me)O–	<0.001	<0.001	—	8	0.004	0.03	31
12	H	$-OCH_2O-$	0.03	0.015	0.015	16	0.03	0.25	0.5
13	H	–OC(O)O–	2	1	4	8	1	2	16
14	H	–OC(S)O–	2	2	8	16	1	125	8
16	H	$-OC(Me)_2CH_2O-$	0.25	0.015	0.12	>125	0.03	1	31
19	α-OH	$-OC(Me)_2O-$	8	2	8	>125	2	31	>125
20[16] (α-anomer)	H	$-OC(Me)_2O-$	4	2	—	>125	4	16	>125
1a	β-OH	Me(E)CH=CH(Z)CH=CHMe	0.25	0.015	0.03	>125	0.03	0.06	0.25

C3′–C4′ bond leads to a significant broadening of the spectrum of action with respect to that of 3′-*O*-substituted derivatives[2,5] (e.g., **1a**, Table 1). All the derivatives synthesised show a high activity against *Candida* spp. In addition, most of them include a moderate activity against *Candida glabrata* (MIC range 8–125 μg/mL) and *C. neoformans* (MIC range 0.5–125 μg/mL). A complete in vitro profile study[15] and activities in experimental therapeutic models[17] of compound **9** have already been reported.

Due to the novel mode of action and the high activity shown by this kind of antifungal agents, further chemical work addressing modifications at other positions of the sordarin structure is planned for the near future.

Acknowledgements

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