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Stereoselective synthesis of the antifungal GM222712

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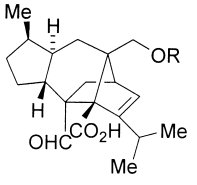
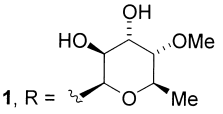
Abstract

An efficient and convergent synthesis of the antifungal agent GM222712 is described. The approach involves the preparation of the modified sugar moiety followed by its stereoselective anomeric *O*-alkylation with sordaricin triflate **19**.

Keywords: antifungals; carbohydrates; radical and radical reactions; alkylation.

Sordarin (**1**) is an antifungal antibiotic discovered by workers at Sandoz in the late 1960's.[1] Among the compounds with sordaricin (**2**) as aglycon, those containing a modified sugar with a fused tetrahydrofuran ring at 3′,4′-positions appear to be the most promising family. Thus, GM222712 (**3**) showed an excellent antifungal profile in terms of both in vitro potency and spectrum of action.[2] Structurally, this compound consists of a 3′-branched chain deoxy sugar linked to **2** through a β-glycosidic bond. In former syntheses, **3** was prepared by a linear approach through chemical modification of a fermentation product.[3] However, this approach was hampered by a low overall yield since **3** was obtained as the minor component of a mixture of two diastereoisomers. We report herein a convergent and more efficient preparation of **3** that involves a new synthesis of the sugar moiety and its β-stereoselective alkylation with a sordaricin triflate derivative.





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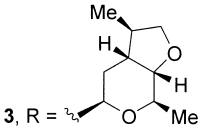
2, R = H



3, R =

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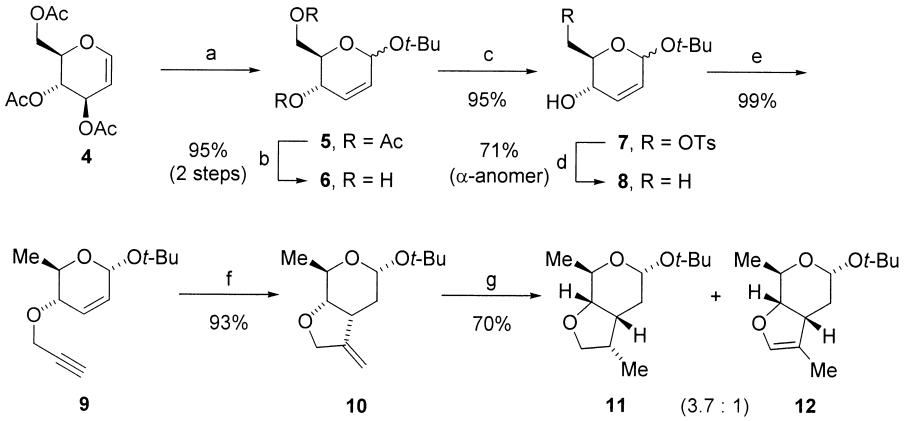
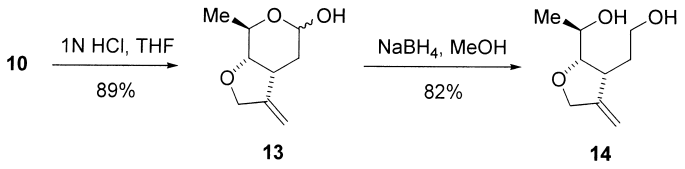
The synthesis started from commercially available 3,4,6-tri-*O*-acetyl-D-glucal (**4**) (Scheme 1). Ferrier rearrangement with *t*-BuOH catalyzed by iodine[4] gave **5** as a 10:1 α:β mixture of anomers. Zemplén deacylation followed by regioselective tosylation of the primary hydroxyl group using tin activation[5] yielded **7**.



Scheme 1. (a) *t*-BuOH, I_2, THF, 0°C to rt. (b) NaOMe, MeOH, rt. (c) i. Bu_2SnO, toluene, 110°C; ii. *p*-TsCl, Bu_4NBr, 60°C to rt. (d) $LiAlH_4$, THF, rt. (e) propargyl bromide, NaH, Bu_4NBr, THF, rt. (f) i. Bu_3SnH, AIBN, toluene, 110°C; ii. AcOH, NaF, rt. (g) H_2, 10% Pd/C, EtOAc, rt

Reduction of **7** with lithium aluminium hydride gave **8**. At this point the two anomers could be separated by chromatography. The α-anomer of **8** was alkylated with propargyl bromide in the presence of tetrabutylammonium bromide to afford **9**. Tributyltin hydride radical cyclization of **9** followed by the in situ protolysis of the alkenyltin intermediate with acetic acid in the presence of KF gave the *cis*-fused tetrahydrofuran derivative **10**. However, hydrogenation of the *exo*-double bond under different conditions took place from the convex face to afford the unwanted *endo*-methyl diastereoisomer **11** and compound **12** resulting from double bond isomerization. To change the sense of the stereoselectivity of this reduction, we tried a hydroxyl-directed hydrogenation.[6] Hydroxyl-directed hydrogenations have only been reported for a restricted range of rhodium and iridium cationic catalysts.[7,8] With this objective, glycoside **10** was hydrolyzed by treatment with 1N aqueous HCl in THF to give hemiacetal **13** (Scheme 2). Reduction of **13** with sodium borohydride afforded diol **14** in quantitative yield. The results obtained for the hydrogenation of **14** under different conditions are shown in Table 1. Both, Pd/C and Wilkinson's catalyst (entries 1–3) led to the preferential addition of hydrogen from the convex face of the molecule to afford mainly the *endo*-methyl diastereoisomer **15** (Scheme 3). However, when $[Rh(nbd)(dppb)]BF_4$ was used

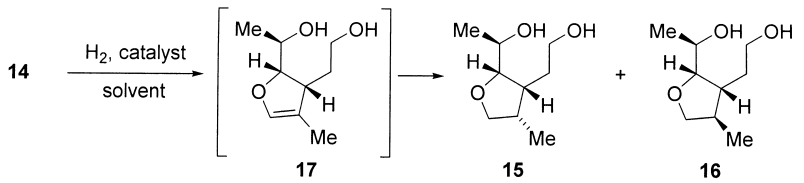


Scheme 2.

Table 1

Entry	Substrate	Catalyst[a]	Mol%	Solvent	Yield	**15** : **16**
1	14	A	10	EtOAc	85	69 :31
2	14	B	100	Toluene	99	94:6
3	14	B	100	CH_2Cl_2	84	93:7
4	14	C	10	CH_2Cl_2	84	24:76
5	14	C	6	CH_2Cl_2	100	10:90
6	14	D	17.5	CH_2Cl_2	—	<1:99
7	14	D	3.6	CH_2Cl_2	74	<1:99
8	14	D	1	CH_2Cl_2	70	<1:99
9	17	A	10	EtOAc	71	95:5
10	17	B	100	Toluene	95	94:6
11	17	D	1	CH_2Cl_2	100	<1:99
12	17	D	0.5	CH_2Cl_2	82	<1:99

[a] A: 10% Pd/C; B: $RhCl(PPh_3)_3$; C: $[Rh(nbd)(dppb)]BF_4$; D: $[Ir(COD)(PCy_3)(Py)]PF_6$

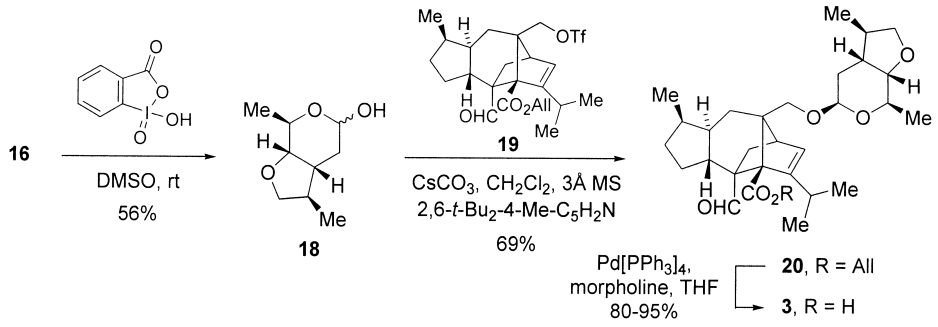


Scheme 3.

(entries 4 and 5), a dramatic change was observed in favor of the desired *exo*-methyl isomer **16**. Complete *exo*-selectivity was achieved with Cabtree's $[Ir(COD)(PCy_3)(Py)]PF_6$ (entries 6–8)[7] with independence of the precatalyst ratio and hydrogen pressure (15–45 psi).

In all the hydrogenation experiments, an intermediate was observed that could be isolated and its structure elucidated. ^{1}H NMR showed the compound to be the *endo*-olefin isomer **17**. Reduction of this compound under the same conditions used for **14** led to similar results (entries 9–12) suggesting that the stereocontrolled hydrogenation of **14** takes place with prior olefin isomerization to **17**. Selective oxidation of the primary hydroxyl group of **16** with *o*-iodoxybenzoic acid[9] reestablished the hemiacetal functionality to give the modified sugar **18** (Scheme 4). Anomeric *O*-alkylation[10] of **18** with the sordaricin allyl ester triflate **19** under our recently established conditions[11] afforded the corresponding glycoside **20** as a separable 1:9 α:β-mixture of anomers. Mild deprotection of the allyl ester of **20** under Pd(0) catalysis finally afforded our target **3**.†

† H NMR data for compound **3** (δ, $CDCl_3$, 300 MHz): 9.87 (s, 1H), 6.04 (d, 1H, J=3.3 Hz), 5.08 (m, 1H), 5.02 (m, 1H), 4.50 (dd, 1H, J=2.7, 8.4 Hz), 4.48–4.29 (m, 3H), 3.76 (dd, 1H, J=7.2, 9.3 Hz), 3.27 (m, 1H), 3.02 (m, 1H), 2.45 (m, 1H).



Scheme 4.

Acknowledgements

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References

1. Sigg, H. P.; Stoll, C. (Sandoz Ltd.): Antibiotic SL2266. UK Patent 1,162,027.
2. (a) Stevens, D. A. 'Screening of Sordaricin Derivatives Against Endemic Fungal Pathogens'. *Poster Session (F-58). 37th ICAAC Meeting, Toronto (Canada)*, **1997**. (b) Herreros, E.; Almela, M. J.; Martínez, C. M.; Lozano, S.; Gómez de las Heras, F.; Fiandor, J. M.; Gargallo, D. 'Sordarin derivatives: Spectrum of Action of a Novel Class of Fungal Protein Synthesis Inhibitors'. *Poster Session. 13th Congress of the ISHAM, Parma (Italy)*, **1997**.
3. Gómez, J. R. R.; Calderón, J. M. B.; García-Ochoa Dorado, S.; Fraile Gabaldón, M. T.; Pichel, J. C.; Fiandor Román, J.; Gargallo Viola, D.; Cueva Zurita, J. C.; Lavandera Díaz, J. L.; Huss, S. Patent WO 96/14326.
4. Koreeda, M.; Houston, T. A.; Shull, B. K.; Klemke, E.; Tuinman, R. J. *Synlett* **1995**, 90–92.
5. Grindley, T. B. *Adv. Carbohydr. Chem. Biochem.* **1998**, 53, 17–142.
6. For a review article on substrate-directable chemical reactions, see: Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307–1370.
7. Cabtree, R. H.; Davis, M. W. *J. Org. Chem.* **1986**, *51*, 2655–2661.
8. Machado, A. S.; Olesker, A.; Castillon, S.; Luckas, G. *J. Chem. Soc., Chem. Commun.* **1985**, 330–332.
9. Corey, E. J.; Palani, A. *Tetrahedron Lett.* **1995**, *36*, 3485–3488.
10. For a recent review on anomeric *O*-alkylation, see: Schmidt, R. R.; Kinzy, W. *Adv. Carbohydr. Chem. Biochem.* **1994**, *50*, 21–123.
11. Coterón, J. M.; Chiara, J. L.; Fernández-Mayoralas, A.; Fiandor, J. M.; Valle, N. *Tetrahedron Lett.* **2000**, *41*, 4373–4377.