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A novel approach to the stereoselective semi-synthesis of GM-237354 by employing a highly β-selective glycosylation

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Abstract—Synthesis of GM-237354 (**1**), a potent inhibitor of fungal elongation factor 2, was achieved starting from sordaricin using a highly stereoselective glycosylation reaction as a key step. Glycosylation utilizing 2-deoxy-2-iodo-glycopyranosyl acetate **6a** gave glycoside **8** as a single product, and **8** was easily converted into **1**. © 2002 Elsevier Science Ltd. All rights reserved.

GM-237354 (**1**) is a potent selective inhibitor of fungal elongation factor 2 (EF-2), and has recently been considered as a promising candidate of novel antifungal agents for the treatment of fungal infection.[1] Whereas **1** was initially prepared from 4′-*O*-demethylsordarin by a semi-synthetic method, several natural congeners have been discovered as members of the sordarin family. Sordarin (**2**) was the first natural product assigned to this class (Fig. 1), and its isolation from the fungus *Sordaria araneosa* was reported in 1971.[2] Since then, zofimarin (**3**),[3] SCH-57404,[4] GR-135402,[5] and BE-31405,[6] which bear a common pharmacophore aglycon, sordaricin (**4**),[7] have become known. However, these compounds showed only weak inhibitory activity against the growth of fungi.

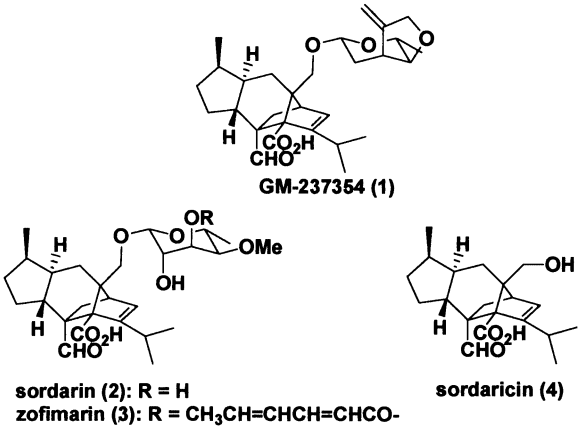

Figure 1. Chemical formulas of GM-237354 and its related compounds.

Furthermore, a number of sordaricin derivatives have been synthesized and disclosed to exhibit similar biological activity.[8–10] Quite recently, others[11,12] and we[13] have described the structure–activity relationships of various types of sordaricin analogues. Unlike known antifungal agents, the mode of action of these sordaricin derivatives is inhibition of fungal protein synthesis[14–16] by selectively binding to the EF-2–ribosome complex of fungi.[17,18] Consequently, this group has been focused on as a novel class of therapeutic antifungal agents. Herein, we describe the semi-synthesis of **1** starting from **4**[19] employing a highly stereoselective glycosylation method utilizing 2-deoxy-2-iodo-glycopyranosyl acetate as a donor.

Initially, we envisaged the strategy using 2-deoxy-2-iodo-glycopyranosyl acetate as the glycosyl donor. This method proposed by Roush et al.[20] is a very efficient way to obtain a pure 2-deoxy-β-glycoside without its anomer. In addition, the glycosyl donor is easily obtained by stereoselective iodoacetylation of D-arabinose as reported by McDonald et al.[21] Therefore, we employed 6-deoxy-3,4-*O*-bis-(*t*-butyldiphenylsilyl)-D-glycal (**5**), prepared in six steps from commercially available tri-*O*-acetyl-D-glycal, as a sugar source.[22]

Treatment of glycal **5** with *N*-iodosuccinimide and acetic acid in toluene afforded a mixture of 2-deoxy-2-iodo-β-glycopyranosyl acetate **6a** and 2-deoxy-2-

Keywords: GM-237354; sordaricin; zofimarin; iodoacetylation; β-selective glycosylation.

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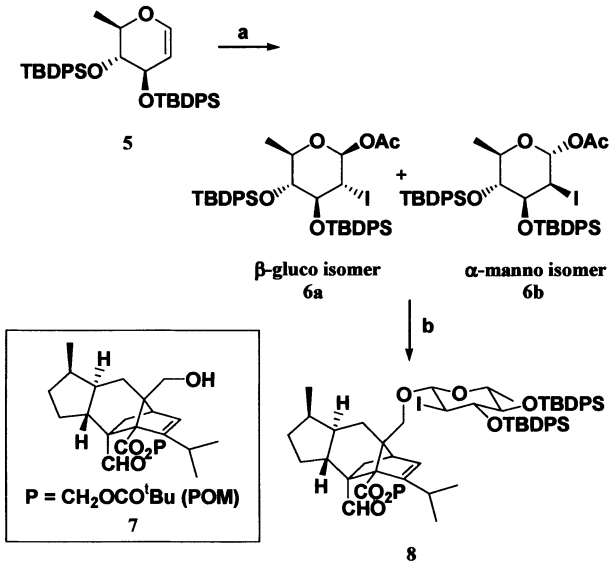
iodo-α-mannopyranosyl acetate **6b** (ca. 9:1) in 99% yield as shown in Scheme 1. Glycosylation of the sordaricin pivaloyloxymethyl (POM) ester (**7**)[23] was smoothly performed with trimethylsilyl trifluoromethanesulfonate (0.25 equiv.) as a promoter at −78°C in dichloromethane (CH_2Cl_2) in the presence of activated 4 Å MS. When **7** was added to the 9:1 mixture (1.2 equiv.), only **6a** was converted furnishing 2-deoxy-2-iodo-β-glycopyranoside **8** as a single product in 90% yield.

As illustrated in Fig. 2, analysis of coupling constants in the ^{1}H NMR spectra suggests that glycal **5** exists not in the *trans*-diequatorial $^4H_5$ conformation, but in the *trans*-diaxial $^5H_4$ conformation due to the repulsion of the vicinal bulky C3 and C4-*O*-(*t*-butyldiphenylsilyl) substituents as described in the literature.[21] Since the reaction was governed by the stereoelectronically favorable *trans*-diaxial addition, **6a** could be obtained with excellent stereoselectivity.

Furthermore, it is known that **6a** exists not in a $^4C_1$ chair conformation but in a twist-boat conformation in order to minimize the *gauche* interaction between the bulky C3 and C4-*O*-(*t*-butyldiphenylsilyl) substituents (Fig. 3).[24,25] This unusual conformation probably induces the high reactivity of **6a**, resulting in the excellent selectivity.[21]

With the β-glycoside **8** in hand, deprotection of the silyl groups of **8** with tetrabutylammonium fluoride (TBAF)



Scheme 1. *Reagents and conditions*: (a) NIS, AcOH, toluene, 110°C, 99%; (b) **7**, TMSOTf, 4 Å MS, CH_2Cl_2, −78°C, 90%.

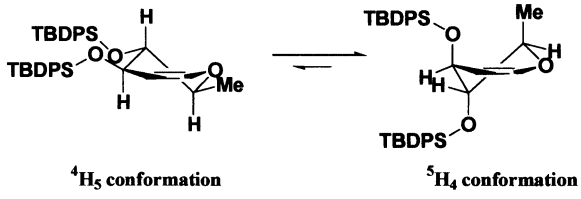


Figure 2. Conformation of 3,4-*O*-bis(*t*-butyldiphenylsilyl)-D-arabinose **5**.

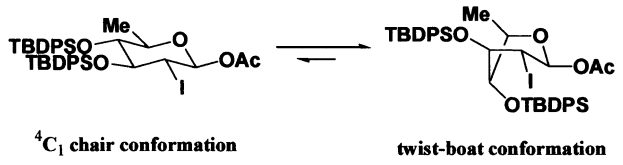
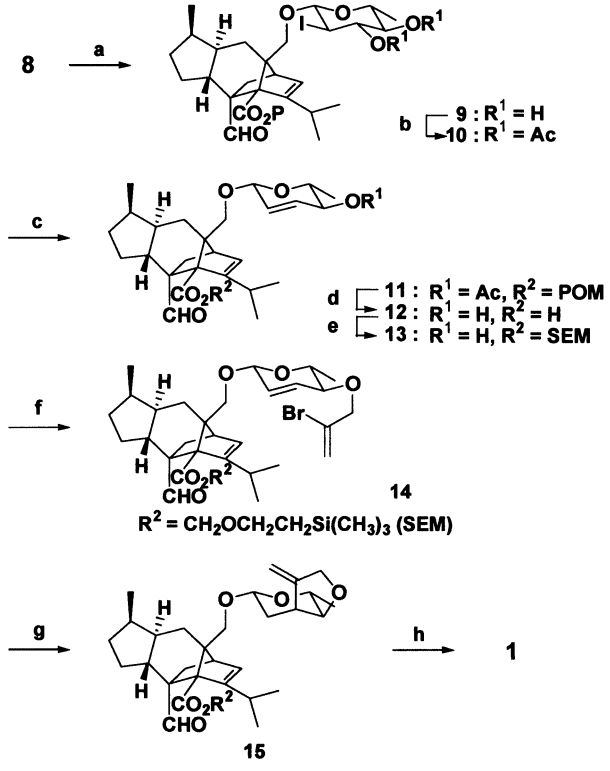


Figure 3. Conformation of 3,4-*O*-bis(*t*-butyldiphenylsilyl) sugar **6a**.

and acetic acid in tetrahydrofuran (THF) gave diol **9** in 67% yield as outlined in Scheme 2. Subsequently, acetylation of **9** with acetic anhydride and pyridine in CH_2Cl_2 provided di-acetate **10** in 94% yield. Treatment of **10** with zinc powder and acetic acid in THF gave rise to olefin **11** in 77% yield. The resulting compound **11** was saponified by sodium methoxide in methanol to produce liberated acid **12** by concomitant deacetylation of the sugar moiety. The carboxylic acid **12** was converted into trimethylsilylethoxymethoxy (SEM) ester **13** in 88% yield (two steps from **11**).

Compound **13** was easily converted to GM-237354 (**1**) according to the patent method[26] as follows. Alkylation of **13** with 2,3-dibromopropene in the presence of cetyltrimethylammonium bromide as a phase transfer catalyst afforded ether **14** in 72% yield. The precursor



Scheme 2. *Reagents and conditions*: (a) TBAF, AcOH, THF, 60°C, 67%; (b) Ac_2O, pyridine, CH_2Cl_2, rt, 94%; (c) Zn, AcOH, THF, 50°C, 77%; (d) NaOMe, MeOH, rt; (e) SEMCl, Et_3N, THF, 0°C, 88% (from **11**); (f) 2,3-dibromopropene, cetyltrimethylammonium bromide, NaOH aq., CH_2Cl_2, rt, 72%; (g) Bu_3SnH, AIBN, toluene, 110°C, 61%; (h) TBAF, THF, 0°C, 80%.

14 was subjected to radical cyclization reaction which was carried out in toluene with 2,2′-azobisisobutyronitrile as an initiator, giving rise to bicyclo product **15** in 61% yield. Finally, deprotection of the SEM ester **15** with TBAF in THF furnished the target compound **1** in 80% yield.

During our ongoing study, the semi-synthesis of **1** from **4** employing anomeric *O*-alkylation was reported.[19] Selectivity is certainly high (α:β = 1:20), however the method gave the corresponding β-glycoside in a moderate yield (71%), containing ca. 5% of undesired α-anomer. Therefore, it is anticipated that purification might be very difficult, especially on a large scale. Our route overcomes this problem. Actually, we obtained the β-glycoside as a single product, needing no severe separation even on a gram scale. This allowed us to easily prepare a large amount of the significant candidate **1** from **4**. In addition, removal of the 2-iodo substituent has been carried out by radical reductive elimination employing tributyltin hydride in the previous reports.[20] To the best of our knowledge, the combination with 1,2-reduction employing zinc powder has been used for the first time. Moreover, the resulting olefin was reacted directly in the later radical cyclization step. This device also widens the importance and utility of the glycosylation reaction, although the reaction itself is a standard method.

In conclusion, we have established a new synthetic route to a potent antifungal agent, GM-237354 (**1**), from sordaricin (**4**) as a starting material. Our synthetic route features the practical application of a highly β-selective glycosylation method, which made it possible to obtain the pure sordaricin β-glycoside without rigorous separation of its anomer. Thus, the route described herein not only made it possible to supply the significant candidate **1** for the biological evaluations, but also is currently being applied to the synthesis of various sordaricin glycosides to search for an improved analogue.

Acknowledgements

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