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Stereocontrolled glycosylation of sordaricin in the presence of ammonium salts

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Abstract

The glycosidation of sordaricin with deoxy sugars derivatives was studied under acid-promoted conditions and by anomeric *O*-alkylation with sordaricin triflate. In both methods, an important effect of added ammonium salts on the stereoselectivity of the glycosidation was observed. © 2000 Published by Elsevier Science Ltd.

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Fungal infections[1] constitute a serious problem for immunocompromised and other vulnerable patients. Sordaricin derivatives **1** and **2** (Fig. 1) are members of a new family of antifungals with a new mode of action. These compounds have demonstrated efficacy in models of systemic infections caused by *Candida* species and endemic American fungi, as well as by *Pneumocystis carinii*.[2] Their chemical structures comprise a diterpene aglycon (sordaricin) and a modified sugar moiety. Currently, these glycosides are prepared following a linear approach starting from natural glycosides.[3] Regarding large scale preparations of **1** and **2**, these syntheses are hampered by the high number of chemical steps and low overall yield in routes that use a fermentation natural product as starting material. Taking advantage of the common aglycon in target molecules **1** and **2**, we planned a convergent approach in which available sugars would be transformed into the appropriate glycosyl donor to be linked to sordaricin in one of the last steps.

The key step of the convergent synthesis is the glycosylation reaction. Although there has been an intensive effort to develop efficient glycosylation methods over the last years,[4] the stereoselective synthesis of 2-deoxy-β-D-glycosides still remains a difficult task. The absence of an auxiliary group at C-2 position makes the stereocontrolled formation of the glycosidic bond difficult to achieve. Most of the methods[5] for the synthesis of 2-deoxy-β-D-glycosides rely on an equatorially installed C-2 heteroatomic substituent that drives the stereochemistry of the glycosylation by

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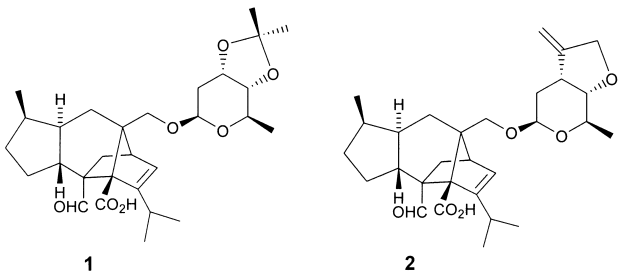
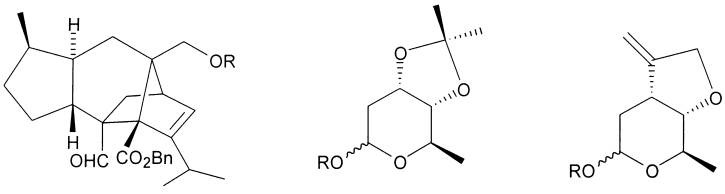


Figure 1.

anchimeric assistance, and which is removed in a later step. In our synthetic scheme, we sought a general method to prepare 2-deoxy-β-D-glycosides of sordaricin without the need of using a substituent temporarily placed at C-2.

In this communication we describe our results on the glycosylation of sordaricin towards the synthesis of **1** and **2**, either by acid-catalyzed glycosylation of sordaricin **3** or by anomeric *O*-alkylation of the sugar with sordaricin triflate **4**.

Acid-catalyzed glycosylation: Three glycosyl donors **6**–**8**, bearing a leaving group at the anomeric position, were prepared from sugar **5** (Fig. 2). For the synthesis of phosphite **6** and trichloroacetimidate **7** we followed described procedures.[6,7] However, both compounds turned out to be highly unstable and could not be isolated. Although we tried 'in situ' glycosylation of alcohol **3** with crude **6** and **7**, erratic results were obtained and, therefore, we focused our attention on the more stable acetate **8** obtained by acetylation of **5**.



3 R = H
4 R = Tf

5 R = H
6 R = $P(OEt)_2$
7 R = $C(NH)CCl_3$
8 R = Ac

9 R = H
10 R = Ac

Figure 2.

The glycosylation reaction of the β-acetate **8** with sordaricin benzyl ester **3** was assayed in the presence of a variety of acid catalysts and under different conditions.† A summary of the results are shown in Table 1. The reaction promoted by $BF_3{\cdot}OEt_2$ afforded a high yield of α- and β-glycosides, though with no stereoselectivity. The change of promoter to $FeCl_3$ or TMSOTf increased the ratio of the nondesired α-glycoside. Interesting results were obtained when a tetrabutylammonium

† Typical procedure: A mixture of **3** (0.1 mmol), acetate **8** (0.12 mmol), Bu_4NBr (0.012 mmol), CH_2Cl_2 and 3 Å molecular sieves was stirred at –78°C for 30 min. After this time, a 0.1 M solution of TMSOTf (0.024 mmol) was slowly added and the stirring was continued at –78°C monitoring the progress of the reaction by TLC (hexane:ethyl acetate 3:1). The reaction was quenched with triethylamine, and, then, filtered through Celite. The filtrate was concentrated and the residue purified by flash chromatography (hexane:ethyl acetate 3:1).

salt was added to the reaction mixture. The presence of the salt led to anomeric mixtures with the β-glycoside predominating. Thus, with $BF_3{\cdot}OEt_2$ and Bu_4NBr the glycosides were isolated in 1:2.2 α:β-ratio. A reversion of the stereoselectivity was obtained with TMSOTf in CH_2Cl_2. While in the absence of Bu_4NBr the α:β ratio was 2.8:1, in the presence of the salt the ratio was 1:2.7 (entries 4 and 7, respectively). The use of iodide instead of bromide salt did not influence the result of the glycosidation (entries 7 and 8). When a 3:1 α,β-mixture of acetates was used as glycosyl donor, no appreciable changes in the course of the glycosidation was observed (entries 5 and 6). This result indicates that the stereoselectivity of the reaction is independent of the anomeric configuration of the starting acetate.

Table 1
Reaction of acetate **8** with sordaricine derivative **3**

Entry	Promoter	Solvent	Additive	Temp. (°C)	Yield (%)	α/β[a]
1	$BF_3{\cdot}OEt_2$	CH_3CN	--	-30	84	1.1:1
2	$BF_3{\cdot}OEt_2$	CH_2Cl_2	--	-20	--[b]	--[b]
3	$FeCl_3$	CH_3CN	--	-30	60	1.8:1
4	TMSOTf	CH_2Cl_2	--	-78	90	2.8:1
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	Bu_4NBr	-20	86	1:2.2
6[c]	$BF_3{\cdot}OEt_2$	CH_2Cl_2	Bu_4NBr	-20	84	1:2.1
7	TMSOTf	CH_2Cl_2	Bu_4NBr	-78	94	1:2.7
8	TMSOTf	CH_2Cl_2	Bu_4NI	-78	86	1:2.8

[a] Ratio of isolated α,β glycosides as determined by ^1H NMR spectroscopy

[b] No reaction was observed

[c] A 3:1 α/β mixture of acetates was used

With the acetate donor **10**, obtained by conventional acetylation of **9**[8] (Fig. 2), the glycosidation of sordaricine **3** was performed using TMSOTf in CH_2Cl_2 giving a 1.2:1 α:β-mixture of glycosides in 91% yield. The addition of Bu_4NBr favoured again the β-glycosidation, although the stereoselectivity was low (α:β ratio = 1:1.6).

The results obtained in the acid-catalyzed glycosidation of **3** with **8** and **10** follow the general trends observed in the construction of 2-deoxy-glycosides: difficult control of the stereoselectivity with predominant formation of the α-glycoside. The present work shows, however, that a certain control of the stereoselectivity in favor of the β-glycoside is possible when the reaction is performed in the presence of Bu_4NBr. This seems to suggest that the glycosylation reaction in the presence of salt proceeds by a double inversion: first the bromide ion displaces the leaving group at the anomeric position, forming a glycosyl bromide which is subsequently displaced by the sordaricin alcohol in a S_N2 mode.

Anomeric O-alkylation: The high β-stereoselectivity normally obtained in the anomeric *O*-alkylation method developed by Schmidt,[9] prompted us to evaluate this method with sordaricin triflate **4**. The influence of solvent, base and of tetrabutylammonium salts was studied.‡ Table 2

‡ Typical procedure for anomeric *O*-alkylation: A solution of triflate **4** (5.9 mmol) in CH_2Cl_2 (45 mL) was added to a mixture of **9** (5.9 mmol), Cs_2CO_3 (7.08 mmol), Bu_4NOTf (0.59 mmol), CH_2Cl_2 (15 mL), and molecular sieves, stirring at room temperature for 20 h (TLC, hexane:ethyl acetate 5:1). The reaction mixture was filtered through Celite, concentrated and the residue was purified by flash chromatography (hexane:ethyl acetate 10:1→7:1).

Table 2
Reaction of sugar **5** with sordaricine triflate **4**

Entry	Solvent	Base	Additive	Yield	α/β[a]
1	THF	NaH	--	50	1:15.0
2	Dioxane	NaH	--	57	1:12.0
3	*t*-BuOMe	NaH	--	38	1:7.5
4	CH_2Cl_2	NaH	--	65	1:6.6
5	THF	Cs_2CO_3	--	17	1:1.2
6	Dioxane	KO*t*-Bu	--	43	1:9.0
7	Dioxane	KO*t*-Bu/ Cs_2CO_3	--	45	1:9.0
8	CH_2Cl_2	KO*t*-Bu	--	75	1:5.4
9	CH_2Cl_2	Cs_2CO_3	--	75	1:3.0
10	CH_2Cl_2	NaH	Bu_4NOTf	58	1:7.0
11	CH_2Cl_2	Cs_2CO_3	Bu_4NOTf	75	1:9.0

[a] Ratio of isolated α- and β-glycosides as determined by ^1H NMR spectroscopy

summarizes the results. Using NaH as base and cyclic ether solvents like THF or 1,4-dioxane, the alkylations proceeded with excellent β-selectivities, though in low yield. Other solvents, such as *t*-BuOMe or CH_2Cl_2, led to a loss of selectivity. The use of weaker bases, KO*t*-Bu or Cs_2CO_3, produced a decrease of the β-selectivity in any of the solvents used (cf. entries 4, 8, and 9). Interestingly, the addition of tetrabutylammonium triflate gave different results depending on the base used. Whereas with NaH as a base the salt did not modify the alkylation result, with Cs_2CO_3 the addition of Bu_4NOTf had a significant effect on the stereoselectivity. Thus, the alkylation in the absence of the salt gave a modest 1:3 α:β-ratio. However, the presence of Bu_4NOTf led to a three-fold increase of the β-selectivity (entries 9 and 11, respectively). These conditions were also applied to the alkylation of **9** with sordaricin triflate **4**, giving the corresponding glycoside in 71% yield and with excellent β-selectivity ($\beta:\alpha > 20:1$).

The effect of Bu_4NOTf on the stereoselectivity is difficult to explain. It could be related to the basicity of the $(Bu_4N)_2CO_3$ salt formed by cation exchange, which could be enhanced with respect to that of Cs_2CO_3 and, therefore, lead to an increase of β-selectivity. Lubineau et al.[10] reported a similar effect of tetrabutylammonium salts on the anomeric *O*-alkylations of sugars. However, in this case the salt shifted the stereoselectivity from β to α.

Following the anomeric *O*-alkylation of **5** and **9** with sordaricin triflate **4**, the benzyl ester was hydrogenolyzed to give glycosides **1** and **2**, respectively.

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