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Glycosylation study on pradimicin–benanomicin antibiotics

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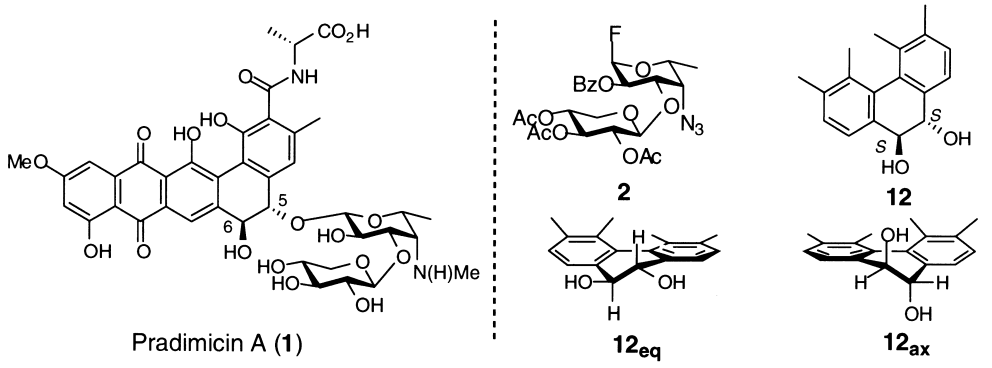
Abstract

In relation to the synthesis of the pradimicin–benanomicin antibiotics, a model study was carried out for introducing the disaccharide moiety. The glycosyl donor **2**, prepared from D-glucose and D-xylose, was allowed to react with various glycosyl acceptors in the presence of Cp_2HfCl_2 and $AgClO_4$. Also studied was the reactivity difference between the conformers of the *trans*-phenanthrendiol derivatives **12**, **13** and **14**.

Our synthetic study on the pradimicin–benanomicin antibiotics (e.g. **1**) is currently focused on two issues for introducing a sugar moiety to the C(5)-hydroxyl of the pentacyclic core.[1,2]

(i) Design of a suitable disaccharide donor.
(ii) Effect of the conformation of the glycosyl acceptor (vide infra).

Described herein is the outcome of our study on these problems. Concerning problem (i), the glycosyl fluoride **2** was prepared, and its reactivity as a glycosyl donor was studied. Problem (ii) dealt with the reactivity difference, if any, between the conformers of the glycosyl acceptor, for which the conformationally-restricted chiral phenanthrendiol **12** and its derivatives were used as the model compounds.



Pradimicin A (**1**)

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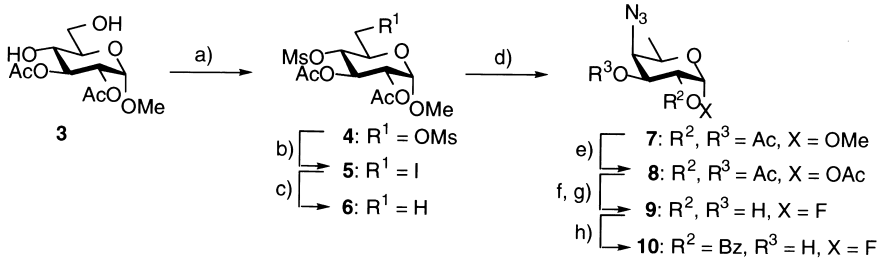
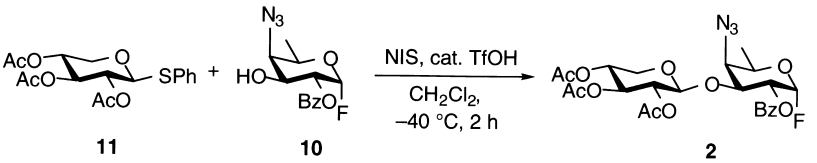
1. Preparation of 2 and its glycosidation study

First, the amino sugar **10** (a D-tomosamine derivative) was synthesized. By the modified procedure of Stevens,[3] the known diol **3**[4] was methanesulfonylated followed by selective displacement of the *prim*-mesylate by iodide to give **5**, and subsequent hydrogenolysis in the presence of NaOAc afforded the 6-deoxy sugar **6**. Treatment of **6** with NaN_3 furnished the azide **7**, which was converted to the glycosyl fluoride **9** by acetolysis followed by treatment with $(HF)_n$·pyr and saponification. Benzoylation of **9** allowed the regioselective protection at 2-OH, giving a mixture of mono-benzoates with predominance of the 2-*O*-benzoyl derivative (2-*O*-Bz:3-*O*-Bz = ca. 8:1). A single recrystallization (EtOAc) gave a pure sample of **10** (mp 124–126°C) in 50% yield (Scheme 1).



Scheme 1. Reagents and conditions: (a) MsCl/pyridine, 15 h (84%); (b) NaI/2-butanone, reflux, 6 h (85%); (c) H_2, 10% Pd–C, NaOAc/EtOH, EtOAc, 15 h (95%); (d) NaN_3, *n*-Bu_4NCl/DMF, 110°C, 10 h (87%); (e) Ac_2O, conc. H_2SO_4, 4 h (91%); (f) $(HF)_n$·pyridine/CH_2Cl_2, –20°C→rt, 8 h; (g) K_2CO_3/MeOH, 0°C, 1 h (two steps, 80%); (h) BzCl/pyridine, 0°C→rt, 15 h (50%)

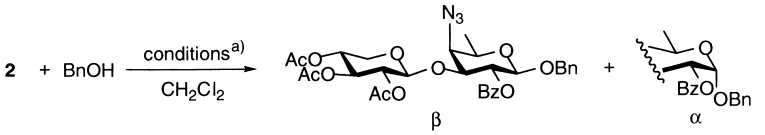


(1)

By exploiting the 'orthogonal glycosylation' by Kanie et al.,[5] the fluoride **10** was glycosylated with the xylosyl sulfide **11**[6] by using NIS and a catalytic amount of TfOH (10 mol%)[7] in CH_2Cl_2 to give the disaccharide **2** in 93% yield (Eq. (1)). The α:β ratio was 1:5, where the requisite β-glycoside was isolated by recrystallization (EtOH, mp 176–178°C).

With the disaccharide donor **2** in hand, the glycosidation was tested with benzyl alcohol as the glycosyl acceptor by using various promoters, and the results are summarized in Table 1. The reaction with $BF_3{\cdot}OEt_2$[8a] or TMSOTf[8b] resulted in complete recovery of **2** (runs 1, 2), which could be ascribed to the deactivation of the promoter by the Lewis-basic functions in **2**. The glycosidation was possible with $SnCl_2$–$AgClO_4$[8c] (run 3), albeit in low yield. Fortunately, the reaction proceeded nicely by employing the zirconocene- or hafnocene-based promoter (runs 4, 5).[9] For example, when the fluoride **2** was allowed to react with benzyl alcohol in the presence of Cp_2HfCl_2 and $AgClO_4$, the glycosylation reaction occurred smoothly (–78 to –20°C), thereby giving the corresponding β-benzyl glycoside in 95% yield.

Table 1
Glycosidation of **2** with benzyl alcohol by using various promoters

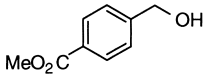
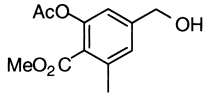


run	promoter (equiv.)	yield / %[d]	β / α
1	$BF_3{\cdot}OEt_2$(1.3)[b]	–	–
2	Me_3SiOTf(1.3)[b]	–	–
3	$SnCl_2$(1.3), $AgClO_4$ (1.3)[b]	16	β
4	Cp_2ZrCl_2(1.3), $AgClO_4$ (2.6)[c]	97	7 / 1
5	Cp_2HfCl_2(1.3), $AgClO_4$ (2.6)[c]	95	β

a) **2** / BnOH = 1 / 1.4; b) –78 to 25 °C, 10 h; c) –78 to –20 °C, 30 min;
d) based on **2**

Under the hafnocene-promoted conditions, thus found, the glycosidation of **2** with various acceptors was tested, where all the reactions listed in Table 2 were complete within 30 min at –20°C.[10] A *sec*-alcohol as well as a *tert*-alcohol can be smoothly glycosylated in high yields (runs 1, 2). The stereoselectivity showed an interesting dependence on the acceptors. A benzyl alcohol with a methoxycarbonyl group was glycosylated with good β-selectivity (run 3), whereas a multi-functionalized orsellinate derivative showed rather poor selectivity (run 4). Interestingly, phenol showed a complete α-selectivity (run 5).[11] It is notable that the reaction stopped at the *O*-glycosylated stage in this case, whereas such reaction conditions usually facilitates the *O*→*C* glycoside rearrangement to give an aryl *C*-glycoside,[12] which could again be ascribed to the diminution of the Lewis acidity by many Lewis basic functionalities.

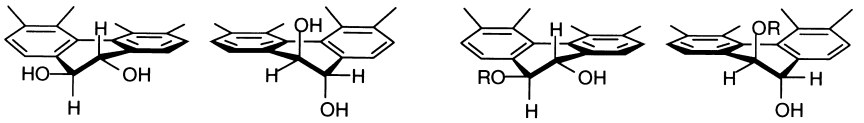
Table 2
Glycosidation of **2** with various acceptors[a]

run	ROH	yield / %	β / α[b]
1	*cyclo*-$C_6H_{11}OH$	91	11 / 1
2	*t*-C_4H_9OH	85	8.4 / 1
3		94	8.7 / 1
4		95	4.2 / 1
5	PhOH	87	α

a) conditions: **2** / ROH / Cp_2HfCl_2 / $AgClO_4$ = 1 / 1.4 / 1.3 / 2.6, MS4A, CH_2Cl_2, –78 °C to –20 °C; b) determined by ^1H NMR (400 MHz).

2. Reactivities of the *trans*-phenanthrendiol derivatives

With these data in hand, we turned our attention to the conformer dependence of the diol acceptor. In order to address this issue, the enantiomerically pure phenanthrendiol (*S*,*S*)-**12**[13] was chosen as the model substrate, because the interconversion of the conformers, **12eq** and **12ax**, is slow enough at ambient temperature, thereby allowing us to examine the reactivity of the conformers as separate entities.[14,15] In addition to **12**, its mono-protected derivatives, **13** and **14**, were tested for this study.



12eq **12ax** **13eq**: R=Ac **13ax**: R=Ac **14eq**: R=Bn **14ax**: R=Bn

Table 3 shows the results of the glycosylation of these compounds with **2** in the presence of Cp_2HfCl_2 and $AgClO_4$. It turned out that the diols **12eq** and **12ax** gave only poor results (runs 1, 2). The diequatorial diol **12eq** showed a poor reactivity, presumably due to the internal hydrogen bonding that makes the hydroxy groups less reactive. On the other hand, the diaxial counterpart **12ax** showed higher reactivity, giving the mono-glycosylated product along with the bis-glycosylated product. Interestingly, all the anomeric centers were β in the mono- as well as the bis-glycosylated product.

Table 3
Glycosylation of various phenanthrendiol derivatives with **2**[a)]

run	substrate	yield / %[b)]	α / β
1	**12eq**	69	1/4.7
2	**12ax**	55 (28)[c)]	β
3	**13eq**	94	1/2.6
4	**13ax**	91	1/4.6
5	**14eq**	94	1/6.7
6	**14ax**	90	1/7.6

a) conditions: **2** / acceptor / Cp_2HfCl_2 / $AgClO_4$=1 / 1.4 / 1.3 / 2.6, MS4A, CH_2Cl_2, –78 °C to –20 °C; b) based on **2**; c) yield of the bis-glycosylated product.

We then examined the glycosylation of mono-protected derivatives, i.e. the acetates **13eq** and **13ax**, and the benzyl ethers **14eq** and **14ax**. Although these compounds were fairly reactive, the stereoselectivity depended on the protecting group. The stereoselectivity was poor for the acetates **13eq** and **13ax** (runs 3, 4), whereas better for the benzyl ethers **14eq** and **14ax** (runs 5, 6). It should be noted that the diaxial conformer consistently showed higher β-selectivity than the diequatorial counterparts.

In summary, we have described a model study for the introduction of a disaccharide moiety in the pradimicin–benanomicin antibiotics, which would hopefully contribute to the completion of the total synthesis. Further work is now in progress in our laboratories.

Acknowledgements

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10. In the presence of Cp_2HfCl_2–$AgClO_4$, the β-xylosyl glycoside undergoes anomerization in the reactions at higher temperature, typically 0°C or above.
11. This result could be rationalized as follows: The β-phenyl glycoside, formed if any, would be more reactive, thereby undergoing a neighboring group-assisted departure of the phenoxide, possibly in a reversible manner, and the less reactive α-glycoside was accumulated.
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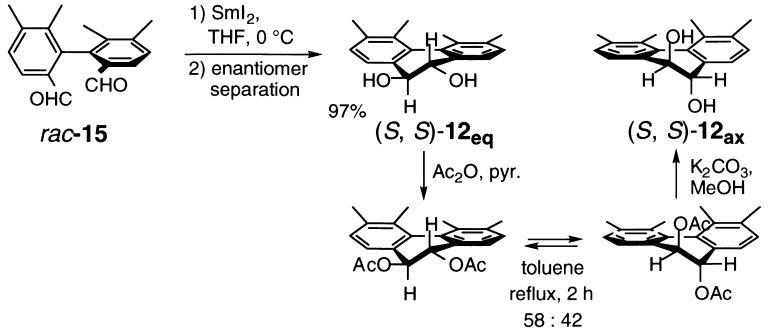
13. Enantiomerically pure (*S*,*S*)-**12eq**[14] was prepared by the SmI_2-promoted pinacol coupling of the corresponding dialdehyde (±)-**15**[16,17] followed by the enantiomer separation by using preparative chiral HPLC column chromatography (Daicel Chiralcel OJ, 20 mm×250 mm, eluted with hexanes:*i*-PrOH = 90:10, flow rate 2.5 mL/min). The CD spectrum showed that the latter fraction was the (*S*,*S*)-enantiomer from the literature data.[15] The corresponding diaxial conformer, (*S*,*S*)-**12ax**, was obtained via the following steps: (1) Ac_2O/pyridine; (2) Δ/toluene; (3) K_2CO_3/MeOH. Partial protection of the hydroxy groups in **12** afforded the mono-protected compounds **13** and **14**.



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