An Improved Practical Method for Synthesis of Aryl *C*-Glycosides from Unprotected Methyl Glycosides and 1-Hydroxy Sugars

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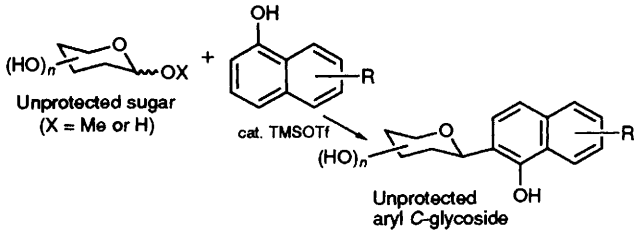
Aryl *C*-glycosidations of the unprotected methyl glycosides **9–12** and the unprotected 1-hydroxy sugars **14** and **15** with 2-naphthol **6** using TMSOTf proceed much more effectively than those of the acylated methyl glycosides **4** and **5**; the unprotected methyl glycoside **10** is also smoothly coupled with other phenol and naphthol derivatives **25–27** to give the corresponding unprotected *o*-hydroxyaryl β-*C*-glycosides in high yields (TMSOTf = trimethylsilyloxytrifluoromethanesulfonate).

Over the past years, aryl *C*-glycoside antibiotics such as aquayamycin **1**, medermycin **2** and vineomycins (vineomycin B_2 **3**) have attracted considerable attention due to their significant biological properties.[1] 2-Deoxy sugars are the most common and important class of sugar residues. Therefore, the effective and practical introduction of the sugar part into the aglycon, the aromatic moiety, has become an important task in organic synthesis. Several methods have already been reported for the synthesis of aryl *C*-glycosides.[2,3] Previously, we demonstrated a novel method for the aryl *C*-glycosidations of acylated methyl glycosides,[4] unprotected methyl glycosides[5] and unprotected 1-hydroxy sugars[5] using TMSOTf–$AgClO_4$ as a combined catalyst. In our studies on this project, we have investigated using a more practical method without $AgClO_4$, which is an unfavourable substance in especially large-scale experiments and industrial processes due to its hazardous and explosive properties. Here, we report that the unprotected methyl glycosides **9–12** and the unprotected 1-hydroxy sugars **14** and **15** were effectively coupled with 2-naphthol **6**, and the unprotected methyl glycoside **10** was smoothly reacted with other phenol and naphthol derivatives **25–27** in the presence of TMSOTf, as the sole catalyst, to afford the corresponding *o*-hydroxyaryl β-*C*-glycosides with high regio- and stereo-control† (Scheme 1).

Since sugars having acyl protecting groups such as acetyl and benzoyl groups could become useful glycosyl donors in a wide variety of glycosidation reactions, we first tried the aryl *C*-glycosidations of the acylated methyl glycosides **4** and **5** with 2-naphthol **6** using only TMSOTf[3d] as the catalyst. The results summarized in Table 1 as entries 1 and 3 showed that the chemical yields of these reactions were much lower than those with TMSOTf–$AgClO_4$ as expected from our previous observations.[4,5] After many attempts to optimize the new catalyst, which has no hazardous or explosive properties, our attention then turned to the effect of the protecting groups of the glycosyl donors. Thus, we next examined the glycosidations of the methylated methyl glycosides **7** and **8** with **6** using TMSOTf. Both the chemical yields and stereoselectivity of these glycosidations were found to be quite satisfactory as shown in Table 1 as entries 2 and 4. Furthermore, unexpected favourable results were obtained for the glycosidations of the corresponding unprotected methyl glycosides **9** and **10** with **6** using TMSOTf. The results illustrated in Table 2 as entries 1 and 2 showed that these glycosidations proceeded much more effectively, than those of the corresponding acylated methyl glycosides **4** and **5** to afford only the unprotected *o*-hydroxyaryl β-*C*-glycosides **21** and **22** in high yields, respectively. These results clearly indicated that unprotected sugars could become very versatile glycosyl donors in the aryl *C*-glycosidation reaction using TMSOTf. We then turned our attention to the scope and limitations of the present method. The results summarized in Table 2 as entries 3 and 4 showed that other unprotected methyl glycosides **11** and **12**, the latter of which is a representative amino sugar and is present in biologically important natural products such as **2**, also reacted with **6** to give high yields of the unprotected aryl β-*C*-glycosides **23** and **24**, respectively. These favourable results prompted us to examine the glycosidations of totally unprotected 1-hydroxy



Scheme 1

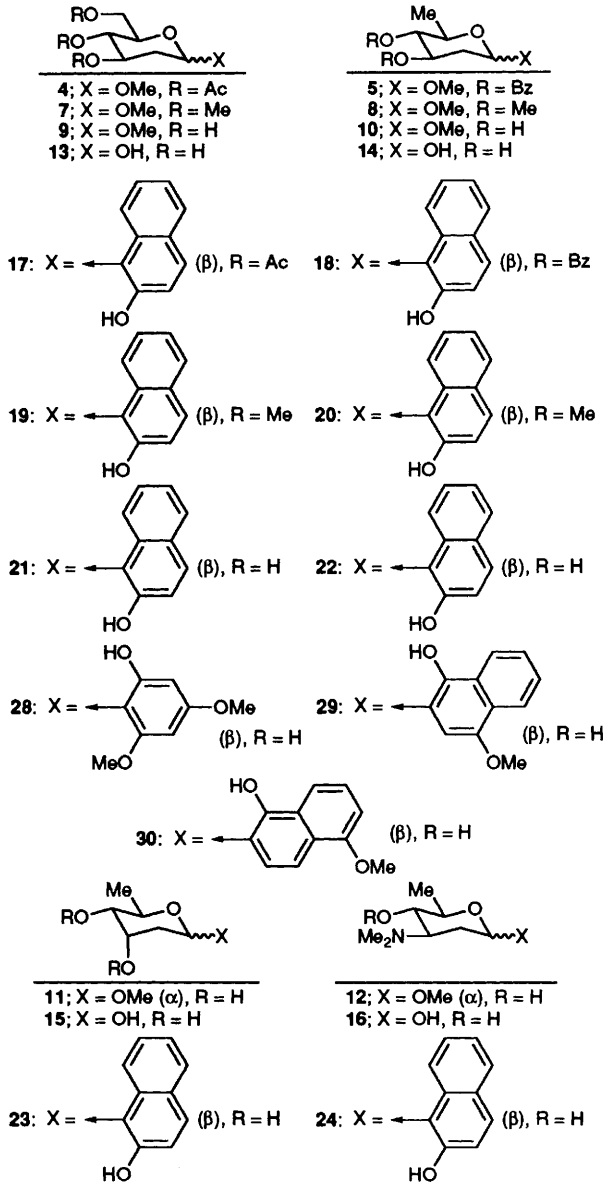


Table 1 Protecting group effect in aryl *C*-glycosidation by TMSOTf[a]

Sugar + **6** $\xrightarrow[25\,°C,\,1\,h]{\text{cat. TMSOTf}}$ Aryl β-*C*-glycoside

Entry	Sugar	Mol% of catalyst	Solvent	Yield[b] (%)
1	**4**	20	CH_2Cl_2	19
2	**7**	20	CH_2Cl_2	99
3	**5**	20	CH_2Cl_2	57
4	**8**	20	CH_2Cl_2	89

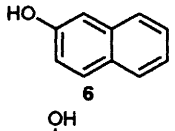
[a] All reactions were carried out using 2-naphthol **6** (2.0 equiv.) to the glycosyl donor. [b] Isolated yields after purification by column chromatography.

Table 2 Aryl *C*-glycosidations of unprotected sugars by TMSOTf[a]

Sugar + **6** $\xrightarrow[CH_2Cl_2\text{ or MeCN}]{\text{TMSOTf}}$ Aryl β-*C*-glycoside

Entry	Sugar	Mol% of catalyst	Solvent	*T*/°C	*t*/h	Yield[b] (%)
1	**9**	50	MeCN	40	1	89
2	**10**	20	CH_2Cl_2	25	1	98
3	**11**	20	CH_2Cl_2	25	1	91
4	**12**	120	CH_2Cl_2	40	8	93
5	**14**	20	CH_2Cl_2	25	1	97
6	**15**	20	CH_2Cl_2	25	1	72

[a] All reactions were carried out using 2-naphthol **6** (2.0 equiv.) to the glycosyl donor. [b] Isolated yields after purification by column chromatography.



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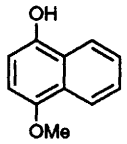

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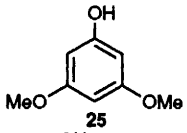

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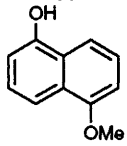

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sugars using this method. Although the glycosyl donors **13** and **16** were not suitable for the present glycosidation reaction due to their low solubility in solvent (MeCN and CH_2Cl_2),[5] both glycosidations of **14** and **15** with **6** in CH_2Cl_2 were effectively achieved under similar conditions to afford the aryl β-*C*-glycosides **22** and **23** with quite satisfactory chemical yield and stereoselectivity (entries 5 and 6 in Table 2). Finally, we tried the aryl *C*-glycosidations of the unprotected methyl glycoside **10** and the unprotected 1-hydroxy sugar **14** with some other

Table 3 Aryl *C*-glycosidations of **10** and **14** by TMSOTf[a]

10 or **14** + Glycosyl acceptor $\xrightarrow{\text{cat. TMSOTf}}$ Aryl β-*C*-glycoside

Entry	Glycosyl donor	Glycosyl acceptor	Mol% of catalyst	Solvent	*T*/°C	*t*/h	Yield[b] (%)
1	**10**	**25**	20	CH_2Cl_2	25	1	98
2	**10**	**26**	20	CH_2Cl_2	25	1	79
3	**10**	**27**	20	CH_2Cl_2	25	1	76
4	**14**	**25**	20	MeCN	25	1	71
5	**14**	**26**	20	MeCN	25	1	63
6	**14**	**27**	20	MeCN	25	1	59

[a] All reactions were carried out using glycosyl acceptor (2.0 equiv.) to the glycosyl donor. [b] Isolated yields after purification by column chromatography.

phenol and naphthol derivatives **25–27**. The results summarized in Table 3 showed that although the yields of the glycosidations of **14** were not very high, all glycosidations of **10** proceeded under mild conditions to afford regio- and stereoselectivity the unprotected *o*-hydroxyaryl β-*C*-glycosides **28–30** in high yields.

In conclusion, the use of TMSOTf gave a significant new method for the effective and practical synthesis of aryl *C*-glycosides from unprotected sugars which should find wide applications even in their large-scale synthesis.

We are grateful to the Institute of Microbial Chemistry for the generous support of our programme.

Received, 7th February 1994; Com. 4/00746H

Footnote

† The α-anomer was not detected by both TLC and ^{1}H NMR analyses in all cases. The structures of all *o*-hydroxyaryl β-*C*-glycosides were assigned from their ^{1}H NMR data which exhibited typical chemical shifts and coupling constants for the β-anomer. The regioselectivity of the glycosidic bond could be derived from the ^{1}H NOE experiments of the aromatic moiety.

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