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Synthetic Studies Directed toward the Assembly of the *C*-Glycoside Fragment of the Telomerase Inhibitor D8646-2-6

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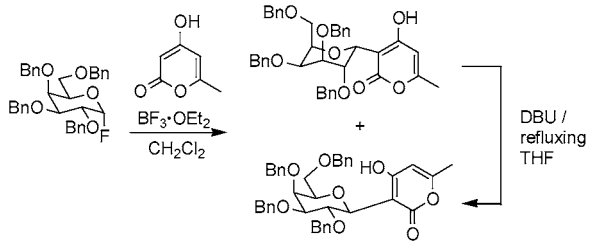
ABSTRACT



Construction and characterization of the C-glycosidic moiety of telomerase inhibitor D8646-2-6 (1) are described. This is the first example of the C-glycosylation using electron-poor aromatics, 4-hydroxypyrone, as a glycosyl acceptor. The glycosylation reaction and base-promoted isomerization affords desired *β*-*C*-glycoside in a 61% overall yield.

D8646-2-6 (**1**) was isolated as an inhibitor of telomerase from the culture broth of *Epicoccum purpurascens* by the Mitsubishi Pharma Corporation group.[1] It has a unique C^3-pyranosyl 4-hydroxypyrone structure with a conjugated heptaene side chain. The relative and absolute stereochemistry of **1** have not been determined. Analysis of the reported ^{1}H NMR data of **1** strongly suggests a C^3-*β*-galactopyranosyl-4-hydroxypyrone structure, although the chirality of the two centers in the side chain is not known. The galactopyranosyl-4-hydroxypyrone structure is quite interesting when compared to *C*-glycosides containing phenol or naphthol derivatives as aryl units.[2] There are some examples of 4-hydroxypyrones connected to a 4-deoxyglucose as sugar moiety, and most of them have antifungal activity.[3] The most challenging step in the synthesis of **1** involves the construction of the pyranosyl 4-hydroxypyrone moiety. The α-pyrone moieties of meroterpenoids (mixed polyketide−terpenoid metabolites) are usually constructed by the cyclization of the corresponding *β*,*δ*-diketo esters.[4] A similar strategy involving the cyclization of α-*C*-pyranosyl *β*,*δ*-diketo ester, which could

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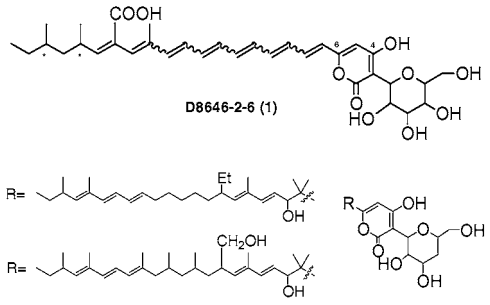
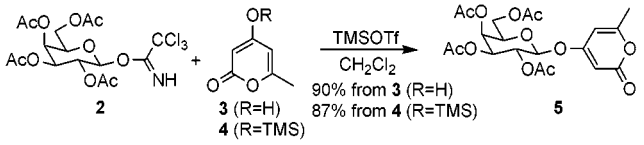


Figure 1. Structure of D8646-2-6 and some examples that contained deoxyglucose as a sugar moiety.

be readily prepared by C-glycosylation of β-ketoester or malonate,[5] might seem like an obvious synthetic route. However, a direct coupling of 4-hydroxypyrone to the sugar moiety is desirable for establishing a convergent and efficient methodology. Despite extensive studies into the C-glycosylation of electron-rich aromatics,[6] there have been no reports concerning C-glycosylation of 4-hydroxypyrone. During the course of our investigations into the synthesis of **1**, we studied the reaction of 4-hydroxypyrone and galactose derivatives. The results of these experiments are described in this paper.

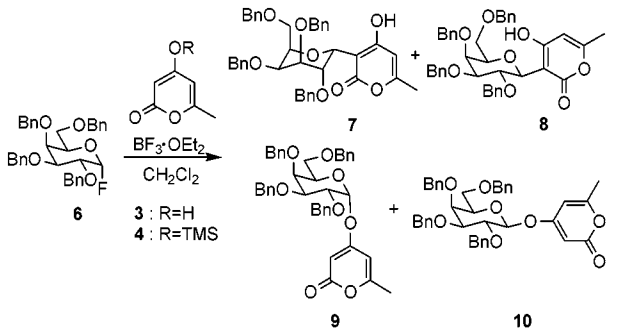
We examined coupling of *O*-(2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranosyl)trichloracetimidate **2**[7] to 4-hydroxy-6-methylpyrone **3** or its TMS ether **4**[8] (Scheme 1). In both

Scheme 1. Glycosylation Reaction between the Trichloroacetimidate **2** and Pyrones **3** and **4**



cases O-glycosylation proceeded smoothly in the presence of TMSOTf in CH_2Cl_2 affording β-*O*-glycoside **5**[9] in high yield (90% for **3** and 87% for **4**), but we could not detect the formation of the desired *C*-glycoside. With an excellent methodology developed by Suzuki in mind, we also attempted an *O*→*C* glycosyl rearrangement[10] of **5** by treatment with Lewis acid. Despite varying the reaction conditions (TMSOTf in CH_2Cl_2, $BF_3{\cdot}OEt_2$ in CH_2Cl_2, $AgClO_4$ in CH_2Cl_2, etc.), none of the desired *C*-glycoside was obtained and, in most cases, almost all of the starting material **5** was recovered. The low reactivity of the *O*→*C* rearrangement could be due to electron-withdrawing acetoxy group at C-2 in **5**. This led us to employ an *O*-benzyl-protected galactose derivative as the glycosyl donor. After a systematic survey of glycosyl acceptors (4-OBn pyrone, 4-OMe pyrone, 4-OTMS pyrone), Lewis acids, and solvents (TMSOTf in CH_2Cl_2/CH_3CN, $BF_3{\cdot}OEt_2$ in CH_2Cl_2/CH_3CN, $SnCl_4$ in CH_2Cl_2, $AlCl_3$ in CH_2Cl_2), we obtained a mixture of both *C*-glycosides (**7** and **8**) and *O*-glycosides (**9** and **10**) by treatment of tetra-*O*-benzyl-D-galactopyranosyl fluoride **6**[11] with 4-hydroxy-6-methylpyrone **3** in the presence of $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Table 1, entry 1). The structures of the *C*-glycosides **7** and **8** were established by ^{1}H NMR analysis. The anomeric proton of the minor glycoside **8** appeared at δ 4.71 with $J = 9.4$ Hz allowing us to determine the β-*C*-glycoside structure. The α-*C*-glycoside structure of the major isomer **7** could not be unambiguously determined from the chemical shift and the coupling constant of the anomeric proton (δ 5.25 as a singlet). However, the strong NOE (7%) between

Table 1. Glycosylation Reaction between the Galactosyl Fluoride **6** and Pyrones **3** and **4**



entry	pyrone (equiv)	$BF_3{\cdot}OEt_2$ (equiv)	solvent	yield (%)		
1	**3** (1)	1	CH_2Cl_2	**7** (15)	**8** (8)	**9**, **10** (15)
2	**3** (3)	1	CH_2Cl_2	**7** (47)	**8** (1)	**9**, **10** (7)
3	**3** (5)	1	CH_2Cl_2	**7** (56)	**8** (5)	**9**, **10** (20)
4	**3** (10)	1	CH_2Cl_2	**7** (54)	**8** (4)	**9**, **10** (21)
5	**3** (5)	1	CH_3CN	**7** (9)	**8** (14)	**9**, **10** (2)
6	**3** (10)	3	CH_3CN	**7** (21)	**8** (16)	**9**, **10** (8)
7	**3** (10)	3	CH_2Cl_2	**7** (36)	**8** (7)	**9**, **10** (37)
8	**4** (5)	1	CH_2Cl_2	**7** (40)	**8** (3)	**9**, **10** (38)
9	**4** (10)	1	CH_2Cl_2	**7** (32)	**8** (trace)	**9**, **10** (46)

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(9) Anomeric proton of **5** appeared at δ 5.20 with $J = 7.9$ Hz.

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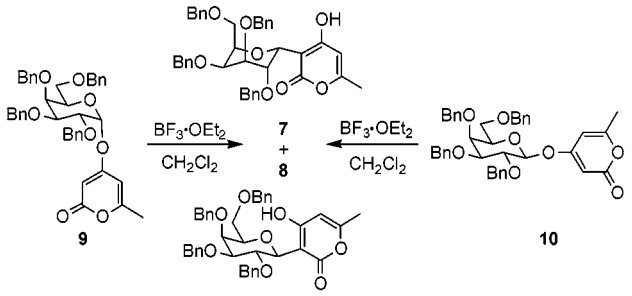
H-1′ and H-2′ and the NOE (8%) between H-1′ and H-6′ unambiguously established the stereochemistry, which indicates that the α-*C*-glycoside **7** adopts the $^1C_4$ conformation with the equatorially oriented pyrone moiety. The yield of *C*-glycoside was improved by using an excess amount of pyrone **3** (Table 1, entry 1−4). In acetonitrile, C-glycosylation did not proceed well, but the desired *β*-*C*-glycoside was obtained in higher yield than in CH_2Cl_2. We think that this selectivity is due to the nitrile effect.[12] When TMS-protected pyrone **4** was used, a considerable amount of O-glycosylation products were formed (Table 1, entry 8−9).

To determine whether *C*-glycoside was formed via *O*-glycoside, **9** and **10** were separately treated with $BF_3{\cdot}OEt_2$ in CH_2Cl_2 (Scheme 2). Interestingly, both **9** and **10** afforded

Scheme 2. Attempted *O*→*C* Glycosyl Rearrangement



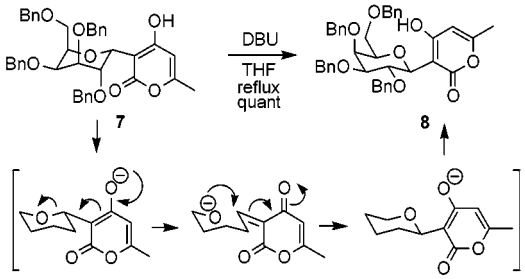
S.M.	Yield (%)		Recovered S.M.(%)
9	**7** (9)	**8** (0)	39
10	**7** (trace)	**8** (1)	66

only a trace amount of *C*-glycoside. Therefore, C-glycosylation and O-glycosylation compete in the case of 4-hydroxypyrone. These results are quite different from glycosylation reactions involving electron-rich aromatics.

The results also show that the Fries-type rearrangement, which proceeded during acylation of 4-hydroxypyrone, did not occur.[13]

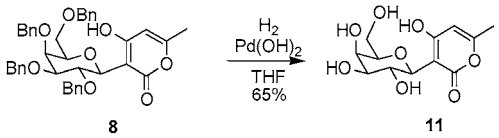
Although the desired *β*-*C*-glycoside was produced as a minor isomer, we found that the α-*C*-glycoside **7** underwent ready and quantitative isomerization[5a,14] with DBU in refluxing THF. Isomerization probably proceeds via base-promoted ring-opening followed by recyclization, giving the thermodynamically more stable *β*-isomer (Scheme 3).

Scheme 3. Isomerization of **7** to **8**



Finally, it was necessary to deprotect **8**. Hydrogenolysis of **8** with $Pd(OH)_2-H_2$ in THF provided **11** in 65% yield (Scheme 4). The ^{1}H NMR and ^{13}C NMR spectral data of **11**

Scheme 4. Hydrogenolysis of the *C*-Glycoside **8**



in CD_3OD were in good accordance with those of **1** except for the differences due to the conjugated side chain moiety.

In summary, glycosylation of 4-hydroxypyrone **3** and galactopyranosyl fluoride **6** provides the first reported synthetic route to C^3-pyranosyl-4-hydroxypyrone. We also observed the base-promoted isomerization of α-*C*-glycoside into the desired *β*-*C*-glycoside **8**. This two-step process affords **8** in a 61% overall yield. Furthermore, the present investigation supports the proposed C^3-*β*-galactopyranosyl-4-hydroxypyrone core structure of **1**.

Application of this method to the total synthesis of **1** is currently in progress.

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Supporting Information Available: Detail experimental procedure, full characterization, and copies of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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