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Synthesis of Novel Ferrocenyl Sugars and their Antimalarial Activities

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Abstract—The synthesis of twelve types of novel ferrocenyl sugars and their biological properties towards the malaria parasite (*P. falciparum*) and mouse cancer cell (FM3A) are described.

Ferrocenes have played an important role in many areas of synthetic and material chemistries.[1] However, only slight attention has been given to their biologically activities,[2] and several references have disclosed the bioactivity of ferrocene derivatives in which the authors reported antitumor-,[3a,e] antiinflammatory-,[3b,c] cytotoxic-,[3d] and DNA cleaving-activity toward cancer cells.[3d] We recently reported the synthesis of artificial ferrocene ellagitannins which contain both the biphenic acid and ferrocene units on the glucose core, (RD)-**1**, (SD)-**1** and **2** (Fig. 1).[4] We now present the initial results of our investigation of the biological properties of various types of novel ferrocenyl sugars.[5]

Four types of 2,3-bridged ferrocenyl cyclic esters of methyl-*O*-glucoside have been synthesized (Scheme 1). The ferrocenyl sugar **4**[4] was treated with ferrocene carboxylic acid and 1,3-dicyclohexylcarbodiimide (DCC) in the presence of 4-*N,N′*-dimethylaminopyridine (DMAP) as the base in dichloromethane (CH_2Cl_2) to give the triferrocenyl ester **5**. The ferrocenyl sugar **4** was reacted with pentaacetyl glucose using boron trifluoride diethyl etherate ($BF_3.OEt_2$) as an activator,[6] and the glycosidation regioselectively took place at the 4-position and afforded ferrocene gentiobiose **6** with perfect β-anomeric selectivity. Glycosidation with 2,3,4,6-pentamethoxy-*O*-phenylthioglucoside[7] gave the easily separable diglycoside **7** and triglycoside **8** as an anomeric mixture.

Other types of ferrocenyl glucosides, **10** and **11**, were prepared from 4,6-*O*-benzylidene glucoside **9** (Scheme 2). Glucoside **9** was treated with 2.2 equivalents of ferrocene carboxyl chloride, which was prepared in situ by the reaction of ferrocene carboxylic acid with oxalyl chloride, in the presence of DMAP at room temperature to give the diferrocenyl glucoside which was then subjected to the deprotection of the benzylidene group to release glucoside **10** (Scheme 2, upper).[8] From glucoside **9**, the regio isomers of the ferrocenyl ester 2-Fc-**11** and 3-Fc-**11** have been synthesized by switching the combination of the base and solvent systems (Scheme 2, middle and bottom).[9] The 2-ferrocenyl ester was obtained when **12** was treated with ferrocenyl chloride in the presence of sodium hydride as the base in toluene, while 3-ferrocenyl ester was obtained when the reaction was carried out using DMAP as the base in CH_2Cl_2. Deprotection of the benzylidene group of these compounds gave 2-Fc-**11** and 3-Fc-**11** in satisfactory yield.

Since an important activity towards human immunity has been reported for ellagitannins,[10] we initially tested the activity of (RD)-**1**, (SD)-**1**, **2** and (RD)-**3** from the viewpoint of immunology. However, no significant activity was obtained, instead they had a toxicity towards the malaria parasite (*P. falciparum*). From ancient times, malaria has posed a serious risk for people living in tropical areas and recently, it has even become a problem in countries in temperate regions.[11,12] It has been reported that ferrocene-chloroquine analogues possess antimalarial activity and this activity increased due to the presence of ferrocene, though the role of ferrocene as enhancer of antimalarial activity was not clear.[13]

The ellagitannin derivative, trideca-*O*-methyl-α-pedunculagin,[9b] which lacked the ferrocene moiety, displayed no

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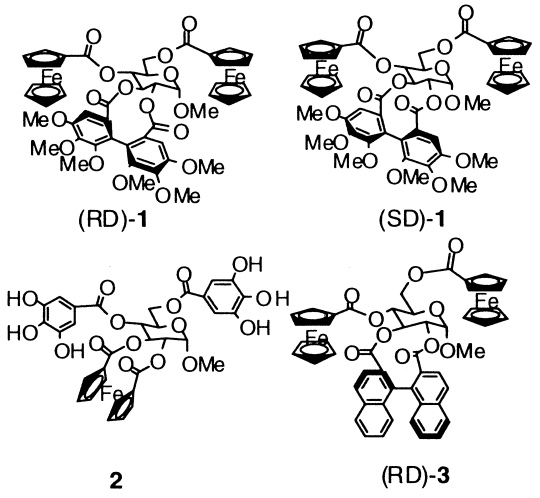
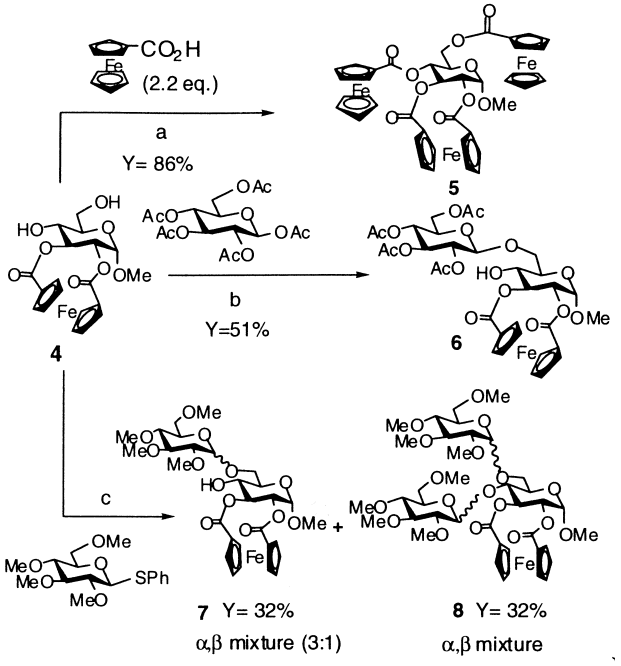
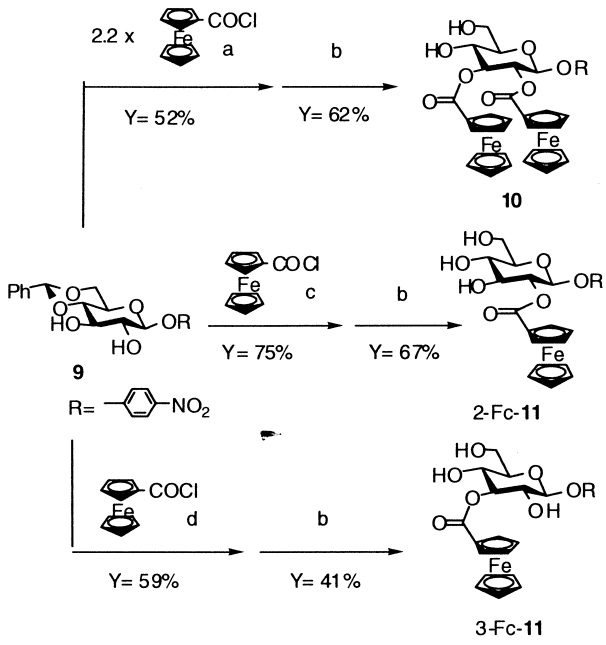


Figure 1. Ferrocenyl sugars.



Scheme 1. Synthesis of bridged type ferrocenyl sugars. (a) DCC, DMAP, CH_2Cl_2, 40 °C 48 h; (b) $BF_3.OEt_2$, CH_2Cl_2, rt 12 h; (c) NBS, CH_3CN-THF, rt 12 h.



Scheme 2. Synthesis of 2-,3-, or 2,3-ferrocenyl glucosides. (a) DMAP (2.2 equiv), CH_2Cl_2, rt 14 h; (b) I_2, MeOH-CH_2Cl_2 (1:1), 50 °C 48 h. 9c) NaH, toluene, 0 °C, 30 min; (d) DMAP (0.2 equiv), Py (3.0 equiv), CH_2Cl_2, rt 12 h.

Table 1. In vitro antimalarial activities[12a] of ferrocenyl sugars against *P. falciparum* and cytotoxicities against FM3ACells

Compound	EC_{50} values (M)		
	P. falciparum[a]	FM3A[b]	Selectivity[c]
(RD)-**1**	1.5×10^{-6}	$>1.8\times10^{-5}$ (78%)[d]	>10
(SD)-**1**	6.0×10^{-7}	$>1.8\times10^{-5}$ (78%)[d]	>25
2	5.0×10^{-6}	$>1.8\times10^{-5}$ (63%)	>5
(RD)-**3**	8.0×10^{-6}	1.3×10^{-5}	5
4	3.8×10^{-5} (84%)[d]	—	
5	$>2.5\times10^{-5}$ (100%)[d]	$>2.5\times10^{-5}$ (100%)[d]	
6	$>2.5\times10^{-5}$ (96%)[d]	$>2.0\times10^{-5}$ (84%)[d]	
7	$>2.8\times1-^{-5}$ (82%)[d]	1.0×10^{-5}	
8	$>1.6\times10^{-5}$ (100%)	$>1.0\times10^{-5}$ (74%)[d]	
10	7.7×10^{-6}	5.6×10^{-6}	1
2-Fc-**11**	$>3.5\times10^{-5}$ (100%)	$>3.5\times10^{-5}$ (68%)[d]	
3-Fc-**11**	$>3.8\times10^{-5}$ (92%)[d]	3.0×10^{-5}	
Quinine	1.1×10^{-7}	1.0×10^{-4}	910

[a]Chloroquine sensitive (FCR-3 strain).
[b]Mouse mammary tumor FM3A cells representing a model of host.
[c]Selectivity = mean of EC_{50} value of FA3A cells/mean of EC_{50} value of *P. falciparum*.
[d]Growth percent at the concentration indicated.

antimalarial activity. In contrast, among the tested compounds, (RD)-**1**, (SD)-**1**, **2**, (RD)-**3** and **10** inhibited the growth of the malaria parasite; (SD)-**1** showed the strongest inhibitory activity which is similar to that of quinine, though the selective toxicity was insufficient (Table 1). The ferrocene moiety, therefore, must have an important function in inhibiting the growth of the malaria parasite. However, the origin of the toxicity towards *P. falciparum* of compound **2** must be due to the galloyl groups at the 4- and 6-positions, because sugars **4** and **5** possess no toxicity. Diferrocenyl glucoside **10** displayed toxicity to both malaria and the mouse cancer cell, while toxicity was significantly less for mono-ferrocenyl glucoside 2-Fc-**11** and 3-Fc-**11**. Therefore, the two ferrocenyl groups at the 2- and 3-positions are obviously important for the inhibitory action. The different levels of toxicity of the 2- and 3-substituted ferrocenyl sugars seem to depend on the ease of degradation of the ferrocenyl group by hydrolysis in the cell; the 2-ferrocenyl sugars may be more easily hydrolyzed than the 3-ferrocenyl sugars in the malaria parasite. It is also noteworthy that disaccharides **6** and trisaccharides **8** displayed no toxicity for either malaria or the mouse cancer cell.

In summary, various types of ferrocenyl sugars were synthesized and their varying toxicity towards the malaria parasite was demonstrated. *This is the first report on investigation of biological activities of ferrocenyl sugars.*

The results obtained suggest that ferrocenyl sugars may become a leading compound for anti-malaria medicine. Further detailed studies of the biological activity of these compounds will reveal their full potential.

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