Redox Active Artificial Ferrocenyl Ellagitannins. Simple Synthesis and Their Electrochemical Properties

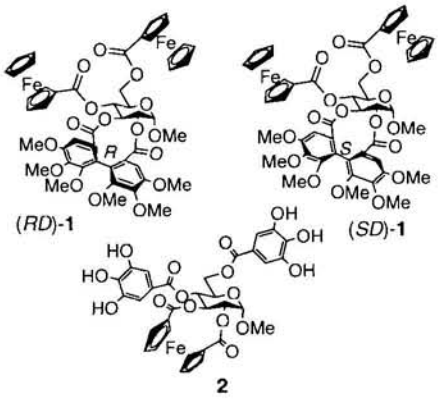
Toshiyuki Itoh,* Shohei Shirakami, Yasuo Nakao, and Takashi Yoshida†
Department of Chemistry, Faculty of Education, Okayama University, Okayama 700-8530
†*Faculty of Pharmaceutical Science, Okayama University, Okayama 700-8530*

(Received June 9, 1998; CL-980440)

Synthesis of three types of novel redox active artificial ferrocenyl ellagitannins has been accomplished in just three steps, and their electrochemical properties have been investigated.

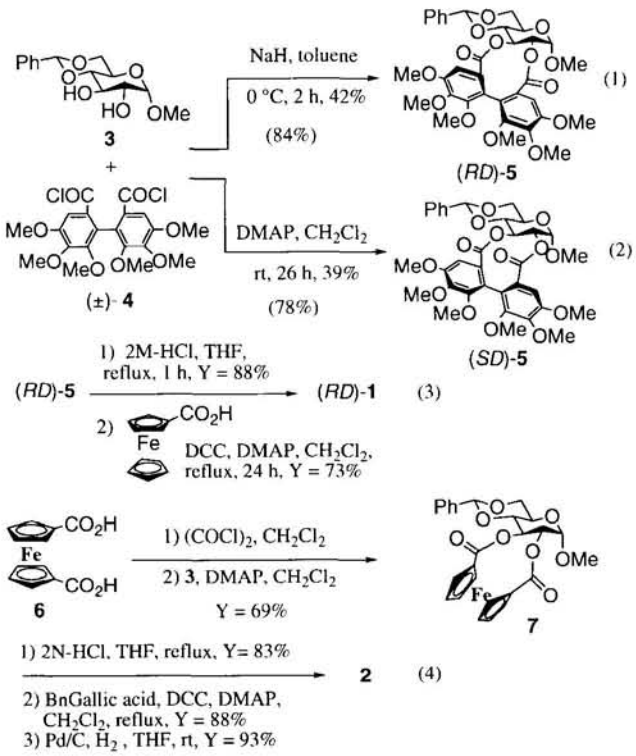
The ellagitannins,[1] which contain at least one axially chiral biphenic acid unit, are found in plants and have been identified as the principal curative and palliative agents in a variety of traditional herbal medicines.[2] Ellagitannins exhibit a wide variety of therapeutically interesting activities such as anti-HIV,[2a] anti-tumor,[2b,2c] and anti-topoisomerase[2d] activity. They have therefore recently been recognized as attractive synthetic targets.[3]

Incidentally, references disclosed that ferrocene has played an important role in many areas of synthetic and material chemistry,[4] and it has been reported that a ferrocene derivative possesses the important biological activity of DNA cleaving towards cancer cells.[5] It is therefore anticipated that the artificial ferrocene ellagitannins which have both biphenic acid and ferrocene units may possess a unique chemical or biological property, though the core source of the biological activity of neither ellagitannins nor ferrocene derivatives is yet clear. We wish to report here the first synthesis of three types of unique novel ferrocenyl ellagitannins (*RD*)-**1**, (*SD*)-**1**, and **2**.



Our strategy for the synthesis of ferrocenyl ellagitannins is a very simple one. We recently reported that esterification of racemic biphenyldicarboxyl chloride with a glucose derivative took place diastereoselectively giving a cyclic ester when reaction conditions were properly chosen.[6] Diastereoselective ester-cyclization of racemic (±)-**4** with glucose derivative **3** at the 2,3-position occurred, and the combination of toluene as solvent and sodium hydride as base provided the cyclized ester (*RD*)-**5** as the sole product with 42% yield; this corresponded to 84% theoretical yield because racemic (±)-**4** was used as the starting material (Eq. 1 in Scheme 1).[7] (*SD*)-**5** was obtained preferentially in 39% yield,[8] this corresponded to 78% theoretical yield, when the reaction was carried out in CH_2Cl_2 in the presence of 4-N,N'-dimethylaminopyridine (DMAP) as base (Eq. 2 in Scheme 1). To apply this methodology, a simple synthesis of ferrocenyl ellagitannins, (*RD*)-**1** and (*SD*)-**1**, was accomplished. As illustrated in Scheme 1, (*RD*)-**5** was obtained diastereospecifically, and following acid treatment, released deprotecting sugar in 88% yield. The resulting sugar was reacted with ferrocenyl carboxyl chlorides at the C4 and C6 positions giving (*RD*)-**1** in 73% yield. Thus, in just three steps, the synthesis of an optically pure new artificial ferrocenyl ellagitannin (*RD*)-**1**, $[\alpha]_D^{22}$ + 85.8 (c 1.07, CH_2Cl_2), was accomplished. Another isomer of (*SD*)-**1**, $[\alpha]_D^{26}$ + 7.8 (c 1.09, CH_2Cl_2),[9] has also been synthesized from (*SD*)-**5** in 61% overall yield (Eq. 3 in Scheme 1).

A different type of ferrocenyl compound **2** has been synthesized; ferrocene dicarboxylic acid **6** was treated with oxalyl chloride to form the corresponding acylchloride *in situ* and reacted with sugar **3** in the presence of DMAP as base in CH_2Cl_2 to give ester **7** in 69% yield. The benzylidene group of **7** was deprotected by treatment with 2M HCl to release diol **8** in 83% yield. Diol **8** was reacted with (3,4,5-tri-O-benzyl)gallic acid in the presence of DCC and DMAP to afford **9** in 88% yield,



Scheme 1. Synthesis of an artificial ferrocenyl ellagitannin **1** and **2.**

and following dehydrogenation to remove the benzyl protecting group gave **2**: $[\alpha]_D^{22}$ + 89.3 (c 0.42, acetone), in 93% yield (Eq. 4 in Scheme 1). This compound was found sensitive to light and acid, and it was rapidly polymerized; compound **2** was gradually changed to an insoluble dark brownish solid if it remained in light under atmospheric pressure at room temperature. This would be due to the oxidative polymerization of the galloyl groups.[10]

Since our novel artificial ellagitannins possess a redox-active subunit, their electrochemical properties were investigated, and representative voltammograms are shown in Figure 1. As anticipated, the anodic electrochemistry is characterized by one-electron oxidation of the ferrocene unit.[11] Because polymerization of **2** was much faster than that of methyl gallate in the presence of dimethyl ferrocene dicarboxylate,[10] the increased current during the oxidation course of **2** seems to be due to intra- or intermolecular electron transfer from the ferrocenyl part to the galloy unit (Figure 1, upper). This result may support the idea that the rapid polymerization of the galloyl units of **2** was accelerated by the intramolecular electron transfer from the ferrocene unit; electron transfer from the ferrocene group caused reduction of the galloyl group of **2** to form an unstable phenoxyl radical species[12] which was easily polymerized by oxygen included in the solvent.[13] The voltammogram of (*RD*)-**1** in acetonitrile showed a reversible couple at +0.80 V vs SCE (Figure 1, lower). No significant difference in the voltammograms between (*RD*)-**1** and (*SD*)-**1** was observed. Therefore, electro-oxidation of the ferrocenyl group of **1** was independent of chirality of the hexamethoxybiphenyl group.

Further studies concerning the biological activity of ferrocenyl ellagitannins are ongoing.

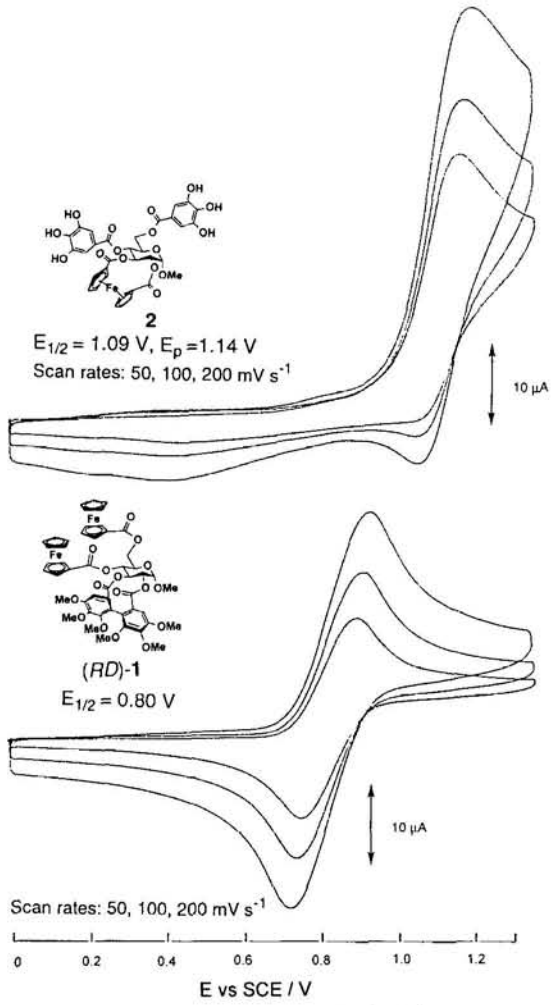


Figure 1. Cyclic voltammograms on (*RD*)-**1** and **2**. Ferrocene 1 mM $TBA^+PF_6^-$ 0.2M in MeCN (24 °C) for **2**, or in CH_2Cl_2 for (*RD*)-**1**.

This work was partially supported by a progress award for students given to SS from the Venture Business Laboratory of the Graduate School of Okayama University.

References and Notes

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7 Only (*RD*)-**5** was obtained and no isomer was detected by HPLC analysis in the reaction.
8 Although (*SD*)-**5** was obtained as major product, 18% (36%) of (*RD*)-**5** was also formed. (*RD*)-**5** and (*SD*)-**5** can be isolated using silica gel flash column chromatography.
9 Anomeric mixture (α: β = 2.7 : 1); the ratio was determined by 200 MHz ^{1}H NMR analysis. Because anomeric epimerization at the C-1 position occurred during deprotection step of the benzylidene group under acidic conditions, and we failed to separate these isomers by silica gel flash column chromatography or silica gel TLC. Interestingly, no epimerization was observed when (*RD*)-**5** was subjected to the same reaction.
10 Methyl gallate was polymerized under ambient atmospheric pressure in acetone in the presence of 1 eq. of dimethyl ester of ferrocene dicarboxylic acid **6**, though more than 5 days was required to complete the reaction.
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