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Synthesis of planar chiral ferrocene dicarboxylic acids using a sugar derivative as a resolution tool

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Abstract

The synthesis of planar chiral ferrocene dicarboxylic acids has been accomplished via diastereoselective esterification at the 2- and 3-positions with (+)-(4,6-*O*-benzylidene)methyl-α-D-glucopyranoside.

1. Introduction

Ferrocenes have played an important role in many areas of synthetic, material and medicinal chemistry.[1,2] They are characterized by remarkably robust stability, display electron transfer properties due to the ferrocene–ferrocenium redox system, and a wealth of methods exist for the system's derivatization.[1] The most important aspect of planar chiral ferrocenes is that of chelating ligands for transition metal-catalyzed asymmetric reactions.[3] Therefore, development of new efficient means for synthesizing planar chiral ferrocenes has been increasingly required. However, only a single example has been reported by Takahashi et al. for the preparation of a planar chiral ferrocene dicarbonyl compound; the authors reported the optical resolution of 2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid **4a** ($R^1 = Ph$, $R^2 = Me$) as its *l*-menthyl ester;[4] however, the absolute configuration of optically active **4a** obtained is still unclear. Herein, we report the resolution of a planar chiral ferrocene dicarboxylic acid via a glucose template-mediated reaction (Scheme 1), and the absolute configuration of 2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid **4a** has been determined for the first time.

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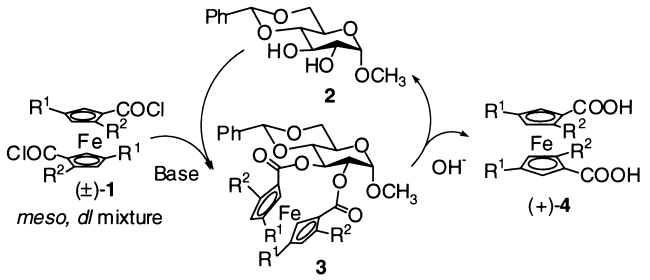
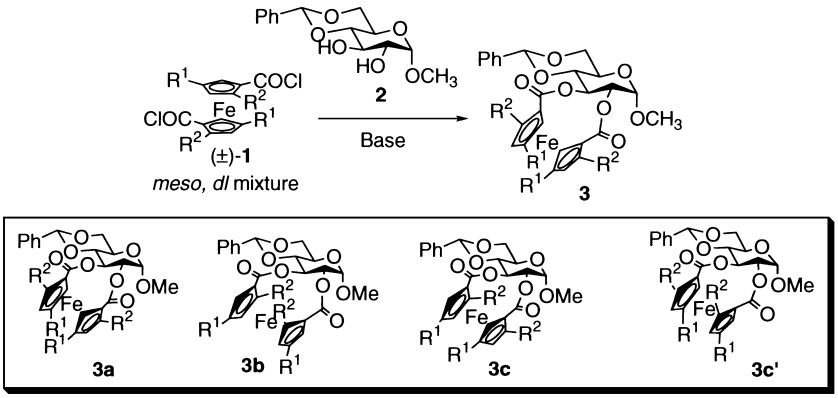


Scheme 1.

2. Results and discussion

We recently demonstrated a simple method for resolving axially chiral biphenyldicarboxylic acids based on the kinetically controlled cyclic ester formation of racemic dicarboxylic acids with (+)-(4,6-*O*-benzylidene)-*O*-methyl-α-D-glucopyranoside **2** by appropriate choice of the reaction conditions.[5] Because the starting planar chiral ferrocene derivative was a mixture of *d,l*- and *meso*-isomers, four types of cyclic esters, **3a**, **3b**, **3c**, and **3c′**, should be produced by the reaction of (±)-**1** and *meso*-**1** with the glucose derivative **2** (Eq. (1)).



(1)

We initially tested the esterification of 2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarbonyl chloride **1a** (R^1 = Ph, R^2 = Me) with glucoside **2** using sodium hydride (NaH) as the base and toluene as the solvent, because this combination of the solvent and base gave the cyclic ester with the best diastereoselectivity when axially chiral diphenic acid chlorides were subjected to the esterification with glucoside **2**.[5] However, the reaction did not provide any of the desired cyclic esters; instead a complex mixture was obtained (Table 1, Entry 1). The desired cyclic esters **3a** (R^1 = Ph, R^2 = Me) and **3c** (R^1 = Ph, R^2 = Me) were obtained when the reaction was carried out in dichloromethane (CH_2Cl_2) as the solvent in the presence of 4-*N*,*N*′-dimethylaminopyridine (DMAP) as the base (Entry 3); cyclic ester **3b** (R^1 = Ph, R^2 = Me) was not obtained, though a fair amount of unidentified oligo- or polymeric compounds was produced. Because the chemical yield of **3a** was 22% which corresponded to an 88% theoretical yield, a highly diastereoselective cyclic esterification was realized. A slightly reduced chemical yield of both cyclic esters **3a** and **3c** was

Table 1
Diastereoselective esterification of **1** with (+)-(4,6-*O*-benzylidene)-*O*-methyl-α-D-glucopyranoside **2**

Entry	R^1	R^2	**2** (eq.)	Base	Solvent (0.01M)	Temp.	Time (h)	Yield (theoretical yield)[a]		
								3a	**3b**	**3c** or **3c'**
1	Ph	Me	1.5	NaH	Toluene	0°C	2	trace	trace	trace
2	Ph	Me	1.5	NaH	Et_2O	0°C~RT	48	trace	trace	trace
3	Ph	Me	1.0	DMAP	CH_2Cl_2	RT	7	22 % (**88%**)	0%	16%
4	Ph	Me	1.0	DMAP	Toluene	RT	10	19% (**76%**)	0%	11%
5	Me	Me	1.0	DMAP	CH_2Cl_2	RT	6	<12% (48%)[b]	<7% (28%)[b]	20%
6	Me	Me	1.0.	DMAP	Toluene	RT	28	<11% (44%)[b]	<15% (60%)[b]	46%

a) Isolated yield. A fair amount of unidentified oligomeric products was obtained. For assignment of the absolute configuration of these cyclic esters, see the text. b) Includes a small amount of the opposite diastereomer because isolation of the diastereomeric pure isomer was unsuccessful by preparative means such as flash column or thin layer chromatography on silica gel.

obtained when the reaction was carried out in toluene as the solvent (Entry 4). On the contrary, the reaction of (±)-**1b** (R^1, R^2 = Me)[6] gave a complex mixture, and isolation of the desired cyclic esters **3ab** (R^1, R^2 = Me) or **3bb** (R^1, R^2 = Me) in diastereomerically pure form was unsuccessful using preparative silica gel chromatography on a flash column or thin layer chromatography (Entries 5 and 6). The cyclic ester formation did not take place at 0°C, and a complex mixture was obtained when the reaction was performed at elevated temperature conditions over 60°C, even for the reaction of **1a** with glucoside **2**. A fine tuning of the reaction conditions was essential in that a very strict combination of the solvent, base, and reaction temperature was required for the diastereoselective cyclic ester formation of ferrocene dicarboxylic acid chloride **1** with glucoside 2. The three-dimensional factor of **1** seems to make it difficult to determine the proper reaction conditions for the present diastereoselective-esterification.

Glucose esters **3a** and **3c** have been obtained in diastereomerically pure forms; the stereochemistry of these compounds was then investigated. We supposed that the ferrocenyl part of **3a** should be assigned to be (*R*,*R*) by ^{1}H NMR analysis on NOE experiments as illustrated in Fig. 1. A significant NOE (3.2%) was observed for the 3-proton on the glucose core with the 2-proton on the *Cp*-ring, and a similar level of the NOE (2.4%) was found for the 1-*O*-methoxy group of the glucose core with the methyl group on the *Cp*-ring. A small NOE (1.0%) was also found for the proton at the benzylidene group with the methyl group on the *Cp*-ring. Based on these results, we tentatively assigned the absolute configuration of the planar chiral ferrocene group of **3a** to be (*R*,*R*).

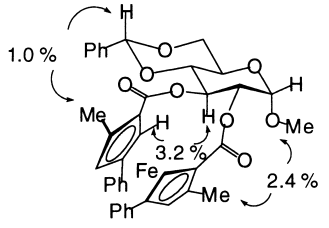
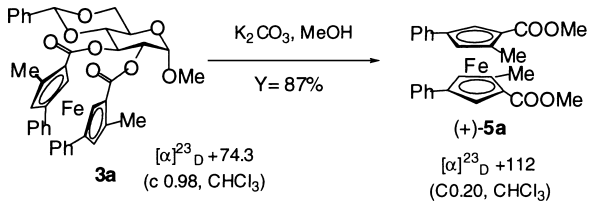


Figure 1. Results of NOE experiments of **3a** (^{1}H NMR)

Because the CD spectra of **3a** were too complicated to analyze the stereochemistry of **3a** regarding the Cotton effect, ester **3a** was converted to ferrocene dicarboxylic acid methyl ester (+)-**5a** (Eq. (2)). Initially, we used a two-step procedure in this process; hydrolysis of **3a** by alkaline treatment (*t*-BuOK, H_2O–THF)[7] to afford dicarboxylic acid **4a** (R^1 = Ph, R^2 = Me), subsequent conversion of **4a** to the corresponding acyl chloride by treatment with oxalyl chloride in situ, and methanolysis of the acyl chloride in the presence of triethylamine to release (+)-**5a** in an acceptable overall yield. However, this procedure sometimes caused a significant loss of the desired ester by formation of insoluble polymeric compounds.[8] Roush et al. reported a very convenient means in which alcolysis of the alkylidene ester of α-hydroxylcarboxylic acid was achieved by the reaction with potassium carbonate in methanol to give the corresponding methyl ester directly.[9] This method was employed for our compound successfully; the methanolysis of **3a** took place very smoothly by treatment with potassium carbonate in methanol to afford the desired methyl ester **5a** in 87% yield (Eq. (2)).



(2)

The CD spectra of (+)-**5a** exhibited a negative chirality regarding the Cotton effect [240 nm and 219 nm ($\Delta\varepsilon$ 21) in CH_3CN; λ_{max} 222 nm, ε 1.01×10^4) (Fig. 2). It was assumed that the Cotton

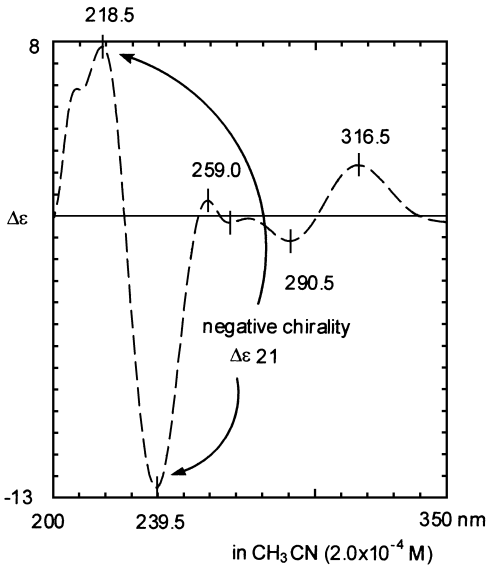


Figure 2. CD spectra of (+)-2,2′-dimethyl-4-4′-diphenylferrocene-1,1′-dicarboxylic acid dimethyl ester (**5a**)

effect of **5a** depended on the three rotary forms, **r-1**, **r-2** and **r-3**, as illustrated in Fig. 3, and different results should be obtained from **r-1**, **r-2**, and **r-3** for the Cotton effect due to the polarity of the carbonyl groups. The opposite results should be obtained from **r-1** and **r-3**, while the CD spectra of **r-2** showed no significant Cotton effect. For example, the **r-1** form of (*R*,*R*)-**5a** should show negative chirality for the Cotton effect; on the contrary, the **r-3** form of (*R*,*R*)-**5a** should show positive chirality. Computational chemistry suggested that **r-1** is the most stable form of **5a** among these three rotatable forms (Fig. 3).[10] A large difference in the heat of formation between **r-1** and **r-3** was found; therefore, it was suggested that the possible form of **5a** should be **r-1** under the usual temperature conditions. Because the negative chirality for the Cotton effect was observed for the CD spectra of **5a**, the absolute configuration of the ferrocenyl part of the glucoside **3a** was assigned to be (*R*,*R*) according to the CD exciton theory.[11] This result agreed with that obtained by an NOE experiment in ^{1}H NMR analysis of **3a**. Determination of the absolute configuration of planar chiral compounds has been a serious problem. It has now become obvious that our methodology provides a good solution to this problem. We can assign the stereochemistry of planar chiral ferrocenyl compounds by the ^{1}H NMR analysis of the corresponding sugar derivatives; this is the very big advantage of our method for the resolution of planar chiral ferrocenyl compounds.

Because ester **3c** was crystallized easily, we attempted to determine the absolute configuration of **3c** by X-ray crystallographic analysis. We initially tried to obtain crystals of **3c** for X-ray analysis; however, obtaining suitable crystals was unsuccessful, though we tested various solvent

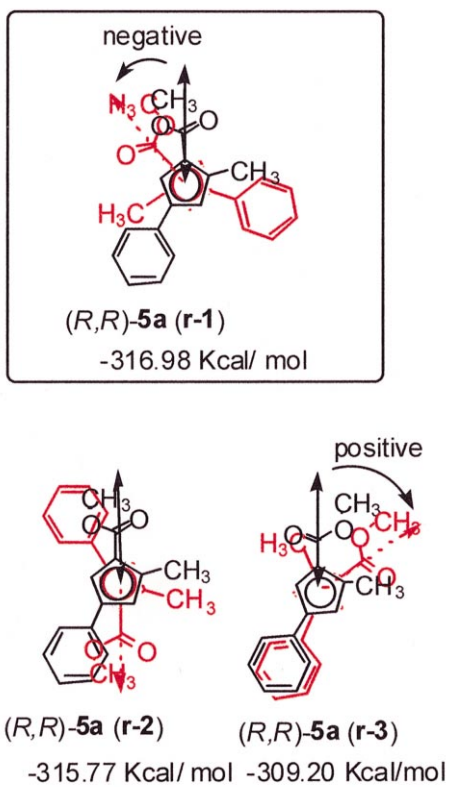


Figure 3. Results of MO (PM3) calculation of three possible conformers of **5a**

systems for recrystallization. Fortunately, we obtained good crystals for the X-ray crystallographic analysis from glucoside **6** which was derived from **3c** by deprotection of the benzylidene group. The ester **3c** was treated with 2 M HCl to release glucoside **6**, and this was recrystallized from benzene and ether to afford red prismatic crystals. Finally, we have succeeded in determining the absolute configuration of glucoside **6** by X-ray crystallographic analysis. The stereochemistry of the ferrocene moiety of glucoside **3c** was thus determined to be (*R*,*S*), the *meso* form, based on the X-ray crystallographic analysis of **6** (Fig. 4).[12]

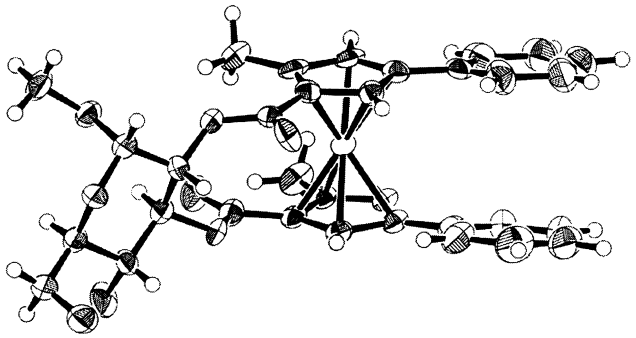


Figure 4. ORTEP view of 2,3-{(*R*,*S*)-(2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarbonyl}-α-D-glucopyranoside (**6**) which was derived from **3c**

3. Conclusions

In summary, planar chiral 2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid methyl ester **5a** has been prepared via the reaction of the corresponding racemic ferrocene dicarbonyl chloride with (+)-(4,6-*O*-benzylidene)-*O*-methyl-α-D-glucopyranoside **2**, and the absolute configuration of (+)-**5a** has been determined. Although there seems to be a limitation for a suitable substrate, the key compound **2** is an inexpensive, commercially available compound, and the reaction can be easily carried out without any special equipment. It should be emphasized that our methodology makes it possible to determine the absolute configuration of the planar chiral ferrocenyl part by ^{1}H NMR analysis of the corresponding glucoside ester. The present methodology should prove to be very useful in the preparation of optically pure planar chiral ferrocenes.

4. Experimental

Reagents and solvents were purchased from common commercial sources and were used as received or purified by distillation over appropriate drying agents. Reactions requiring anhydrous conditions were run under an atmosphere of dry argon. Silica gel (Wako gel C-300, 300E) was used for column chromatography and silica gel (Wako gel B-5F) for thin layer chromatography. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian VXR-200 (200 MHz) spectrometer, and chemical shifts are expressed in ppm downfield from tetramethylsilane (TMS) in $CDCl_3$ as an internal reference.

4.1. 4,6-O-Benzylidene-2,3-{(R,R)-(2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarbonyl}-O-methyl-α-D-glucopyranoside **3a**

2,2′-Dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid[4] (a mixture of *dl* and *meso* forms) (1.45 g, 3.19 mmol) was treated with oxalyl chloride (1.62 g, 12.8 mmol) in benzene (30 ml) under reflux conditions for 12 h, and the solvent was removed under vacuo to afford acid chloride (±)-**1a** (1.56 g) which was used immediately without purification for the esterification with glucoside **2**. To a solution of **1a** (1.56 g) in CH_2Cl_2 (300 ml) was added glucoside **2** (1.26 g, 4.47 mmol, >99% ee) and DMAP (1.17 g, 9.57 mmol) at 0°C, and the mixture was stirred at room temperature for 23 h. The reaction was quenched by the addition of crushed ice and then extracted with ethyl acetate. The combined organic layer was dried ($MgSO_4$), evaporated, chromatographed on a silica gel flash column (hexane:ethyl acetate = 10:1 to 5:1) and gave cyclic esters (1.62 g, 1.46 mmol). Ester **3a** (492 mg, 0.77 mmol, 22%) and **3c** (358 mg, 0.51 mmol, 16%) were isolated by silica gel thin layer chromatography after seven developments (hexane:ether = 7:1), respectively. Results of HPLC analysis (ChiralcelOD, hexane:*i*-PrOH (15:1), 1.0 ml/min, 30°C): *t*R 37.3 min (**3a**), *t*R 48.8 min (**3c**).

Compound **3a**: $[\alpha]_D^{23} = +74.3$ (*c* 0.98, $CHCl_3$); mp 168–170°C, recrystallized from benzene; R_f 0.42, hexane:ethyl acetate = 4:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.53 (3H, s), 1.54 (3H, s), 3.51 (3H, s), 3.85 (1H, dd, J = 10.2, 4.0 Hz, Glc-H_{6a}), 3.90 (1H, dd, J = 9.9, 4.0 Hz, Glc-H_{6b}), 4.00–4.15 (1H, m, Glc-H_5), 4.36 (1H,dd, J = 10.2, 4.3 Hz, Glc-H_4), 4.51 (1H, d, J = 1.6 Hz, Fc-H_3), 4.54 (1H, d, J = 1.6 Hz, Fc-$H_{3'}$), 4.83 (1H, d, J = 1.7 Hz, Fc-H_5), 4.91 (1H, d, J = 1.7 Hz, Fc-$H_{5'}$), 4.95 (1H, d, J = 3.5 Hz, Glc-H_1), 5.38 (1H, dd, J = 10.0, 3.5 Hz, Glc-H_2), 5.57 (1H, s), 5.88 (1H, dd, J = 10.0, 9.9 Hz, Glc-H_3), 7.26–7.55 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 10.8, 11.0, 55.4, 63.6, 68.6, 69.0, 69.5, 70.9, 72.2, 72.9, 73.1, 77.2, 79.2, 90.7, 91.1, 92.0, 92.5, 99.1, 101.7, 126.7, 126.3, 127.4, 128.2, 128.7, 129.1, 134.2, 134.3, 136.9, 171.3, 172.1; IR (KBr) 3222, 1718, 1409, 1230, 1076, 761 cm^{-1}. Anal. calcd. for $C_{40}H_{36}FeO_8$: C, 68.58; H, 5.18. Found: C, 69.57; H, 5.84.

4.2. 4,6-O-Benzylidene-2,3-{(R*,S*)-(2,2′-dimethyl-4,4′-diphenylferrocene-1,1′-dicarbonyl}-O-methyl-α-D-glucopyranoside **3c**

$[\alpha]_D^{23} = +145.6$ (*c* 1.17, $CHCl_3$); mp >200°C, recrystallized from CH_2Cl_2; R_f 0.45, hexane:ethyl acetate = 4:1; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.10 (3H, s), 2.38 (3H, s), 3.50 (3H, s), 3.84 (1H, dd, J = 10.2, 2.0 Hz, Glc-H_{6a}), 3.89 (1H, dd, J = 9.2, 2.0 Hz, Glc-H_{6b}), 4.04 (1H, d, J = 1.7 Hz, Fc-H), 3.81–4.12 (1H, m, Glc-H_5), 4.36 (1H, dd, J = 10.0 Hz, 4.3 Hz, Glc-H_4), 4.82 (1H, d, J = 1.7 Hz, Fc-H), 4.87 (1H, d, J = 1.7 Hz, Fc-H), 4.97 (1H, d, J = 3.5 Hz, Glc-H_1), 5.21 (1H, d, J = 1.7 Hz, Fc-H), 5.46 (1H, dd, J = 10.3, 3.5 Hz, Glc-H_2), 5.57 (1H, s), 5.86 (1H, dd, J = 10.3, 10.0 Hz, Glc-H_3), 6.92–7.52 (15H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 10.7, 13.6, 55.5, 63.8, 69.0, 69.7, 70.5, 71.0, 73.0, 73.8, 74.2, 75.9, 79.2, 88.5, 89.0, 90.4, 92.9, 99.1, 101.8, 125.5, 125.8, 126.4, 126.7, 126.8, 128.2, 128.4, 129.1, 134.2, 136.9, 170.0, 172.8 ppm; IR (KBr) 2924, 1712, 1230, 1070, and 760 cm^{-1}. Anal. calcd. for $C_{40}H_{36}FeO_8$: C, 68.58; H, 5.18. Found: C, 69.59; H, 5.86.

4.3. (R,R)-(+)-2,2′-Dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid dimethyl ester **5a**

To a methanol (4 ml) solution of the (+)-glucoside **3a** (21.0 mg, 0.030 mmol) was added potassium carbonate (25 mg, powder), and the mixture was stirred for 40 h at room temperature. To this mixture was added saturated NH_4Cl aqueous solution (1 ml) and extracted with ethyl

acetate. The combined organic layers were dried ($MgSO_4$), evaporated, and silica gel flash column chromatography (hexane:ethyl acetate = 40:1 to 10:1) gave (+)-**5a** (12.5 mg, 0.026 mmol) in 87% yield. $[\alpha]_D^{24} = +112$ (*c* 0.20, $CHCl_3$); mp >250°C (decomposed); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.09 (6H, s), 3.62 (6H, s), 4.44 (2H, d, J = 1.7 Hz), 4.95 (2H, d, J = 1.7 Hz), 7.21 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 12.8, 51.3, 70.0, 72.3, 74.0, 87.9, 89.4, 125.9, 126.7, 128.4, 134.5, 170.5; IR(KBr) 3024, 2951, 1713, 1442, 1237, 1078, 769 cm^{-1}. Anal. calcd. for $C_{28}H_{26}FeO_4$: C, 69.72; H, 5.43. Found: C, 69.26; H, 5.60.

4.4. (meso)-(S,R)-(+)-2,2′-Dimethyl-4,4′-diphenylferrocene-1,1′-dicarboxylic acid dimethyl ester **5c**

(*meso*)-**5c** was obtained from glucoside **3c** by the same procedure as described above. Mp 160–162°C, recrystallized from CH_2Cl_2; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.02 (6H, s), 3.66 (6H, s), 4.41 (2H, d, J = 1.7 Hz), 4.89 (2H, d, J = 1.7 Hz), 7.21–7.29 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 12.6, 51.3, 70.8, 72.3, 74.2, 87.8, 89.2, 125.9, 126.8, 128.5, 134.8, 170.7; IR(KBr) 3024, 2951, 1712, 1442, 1237, 1078, and 768 cm^{-1}. Anal. calcd for $C_{28}H_{26}FeO_4$: C, 69.72; H, 5.43. Found: C, 69.26; H, 5.60.

4.5. 2,3-{(R,S)-(2,2′-Dimethyl-4,4′-diphenylferrocene-1,1′-dicarbonyl}-α-D-glucopyranoside **6**

A mixture of ester **3c** (29 mg, 0.040 mmol) in 2 M HCl (3.0 ml), methanol (2.0 ml), and THF (5.0 ml) was heated to reflux for 1 h. After cooling to room temperature, the mixture was neutralized by the addition of $NaHCO_3$ saturated aqueous solution and extracted with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness. Silica gel flash column chromatography (hexane:ethyl acetate:methanol = 3:1:0 to 3:1:1) gave **6** (22 mg, 0.36 mmol, 90%). Glucoside **6** (22 mg) was then recrystallized from benzene and ether (4:1) to afford red prismatic crystals (12 mg). $[\alpha]_D^{24} = +245$ (*c* 0.92, acetone); mp >250°C (decomposed); ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.00 (1H, brs), 2.02 (3H, s), 2.31 (3H, s), 2.46 (1H, d, J = 4.2 Hz), 3.42 (3H, s), 3.79–3.90 (4H, m), 3.97 (1H, d, J = 1.7 Hz), 4.75 (1H, d, J = 1.6 Hz), 4.80 (1H, d, J = 1.7 Hz), 4.88 (1H, d, J = 3.5 Hz), 5.10 (1H, d, J = 1.6 Hz), 5.30 (1H, dd, J = 10.3 Hz, 3.4 Hz), 5.52 (1H, dd, J = 10.3 Hz, 8.4 Hz), 6.83–7.19 (10H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 11.0, 13.5, 55.4, 62.1, 69.1, 70.0, 70.1, 70.2, 72.3, 73.1, 73.3, 74.1, 74.2, 75.8, 77.2, 88.4, 88.9, 90.7, 92.6, 98.2, 125.4, 125.8, 126.7, 126.8, 128.4, 134.0, 171.3, 172.6 ppm; IR (KBr) 3525, 3394, 2925, 1707, 1411, 1234, 1074 cm^{-1}. Anal. calcd. for $C_{33}H_{32}FeO_8$: C, 64.72; H, 5.27. Found: C, 64.73; H, 5.33.

Crystal and refinement data for **6**: $C_{33}H_{32}FeO_8$, formula weight = 612.46, monoclinic, space group $P2_1$ (#4), $a = 13.3560$ Å, $b = 7.7419$, $c = 14.0370$ Å, $V = 1416.37$Å^3, $Z = 2$, $d_{calc} = 1.436$ g cm^{-3}, $R(Rw) = 0.059$ for 2535 diffraction data with $I > 3.00\sigma(I)$ and 379 variable.

4.6. 2,2′,4,4′-Tetramethylferrocene-1,1′-dicarboxylic acid ethyl ester **5b**

A mixture of 2,4-dimethylcyclopentadiene-1-carboxylic acid ethyl ester[4] (729 mg, 4.39 mmol), iron(II)chloride (278 mg, 2.20 mmol), and diethylamine (642 mmol, 8.78 mmol) was stirred for 4 days at room temperature, and the reaction was quenched by addition of 2 M HCl (5 ml) at 0°C. The mixture was extracted with ether, and the combined organic layers were dried over $MgSO_4$ and evaporated to dryness. Silica gel flash column chromatography (hexane:ethyl acetate = 50:1 to 30:1) gave **5b** (353 mg, 0.91 mmol) in 42% yield as a red solid. The starting ester (156 mg, 21%) was recovered. R_f 0.46, hexane:ethyl acetate = 7:1; mp 38°C, recrystallized from ether; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.31 (3H, t, J = 7.1 Hz), 1.32 (3H, t, J = 7.1 Hz), 1.80 (3H, s), 1.83 (3H, s),

2.05 (6H, d, J = 2.1 Hz), 4.03 (2H, brs), 4.21 (4H, dq, J = 7.1, 2.1 Hz), 4.42 (1H, brs), 4.51 (1H, brs); ^{13}C NMR (50 MHz, $CDCl_3$) 12.95, 13.02, 14.42, 59.78, 86.92, 87.84, 171.3; IR (KBr) 3050, 2970, 1700, 1410, 1210, 1070, 770 cm^{-1}. Anal. calcd. for $C_{20}H_{26}FeO_4$: C, 62.19; H, 6.78. Found: C, 62.80; H, 6.93.

4.7. 2,2′,4,4′-Tetramethylferrocene-1,1′-dicarboxylic acid **4b**

To a solution of potassium *t*-butoxide (557 mg, 4.96 mmol) in a mixed solvent of THF (20 ml) and H_2O (89 mg) was added ethyl ester **5b** (239 mg, 0.62 mmol) at room temperature, and the mixture was stirred for 24 h at room temperature. The reaction was quenched by addition of 2 M HCl (10 ml) with stirring for 30 min at room temperature, then extracted with $CHCl_3$. The combined organic layers were dried ($MgSO_4$) and evaporated to dryness, and the resulting red solid was washed with ether several times to afford acid **4b** (185 mg, 0.56 mmol) in 91% yield. R_f 0.52, CH_2Cl_2:methanol = 10:1; mp > 250°C (decomposed); IR (KBr) 3050, 2950, 2700, 1680, 1440, 1250, 710 cm^{-1}. Anal. calcd. for $C_{16}H_{18}FeO_4$: C, 58.21; H, 5.50. Found: C, 53.23; H, 5.36. Because this compound was insoluble in $CDCl_3$, DMSO-d_6, CD_3OD, and CD_3COCD_3, we gave up trying to do the NMR analysis.

4.8. 2,2′,4,4′-Tetramethylferrocene-1,1′-dicarbonyl chloride **1b**

To a mixture of acid **4b** (585 mg, 1.77 mmol) and $(COCl)_2$ (899 mg, 7.08 mmol) was added benzene (20 ml) and the mixture stirred for 7.5 h under reflux conditions. The solvent was removed to dryness under reduced pressure to give **1b** (670 mg, 1.68 mmol) in 95% yield. IR(KBr) 2920, 1751, 1448, 1379, 1254, 808 cm^{-1}. This was used for the next esterification with glucoside **2** without further purification.

4.9. 4,6-O-Benzylidene-2,3-{(R,R)-(2,2′,4,4′-tetramethylferrocene-1,1′-dicarbonyl}-O-methyl-α-D-glucopyranoside **3ba**

Glucoside ester (+)-**3ba** was obtained by the reaction of racemic **1b** with glucoside **2** by the same procedure as described above. However, it was impossible to isolate each of the cyclic esters of **3ba**, **3bb** in diastereomerically pure form by preparative methods using silica gel flash column or thin layer chromatography (TLC). We isolated **3ba** and **3bb** by silica gel TLC by 31 times developments (hexane/ ether = 8:1). **3ba**: $[\alpha]_D^{22} = +276$ (*c* 0.90, $CHCl_3$); Rf 0.46, hexane/ethyl acetate = 4:1; mp > 200°C, recrystallized from ether; ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.91 (3H, s), 2.00 (3H, s), 2.04 (3H, s), 2.22 (3H, s), 3.46 (3H, s), 3.76–3.89 (3H, m, Glc-H_6, Fc-H_3), 4.02 (1H, dt, J = 9.7 Hz, 4.3 Hz, Glc-H_5), 4.15 (1H, d, J = 1.7 Hz, Fc-H_3), 4.33 (1H, dd, J = 9.8 Hz, 4.3 Hz, Glc-H_4), 4.55 (1H, d, J = 1.6 Hz, Fc-H_5), 4.60 (1H, d, J = 1.7 Hz, Fc-H_5), 4.90 (1H, d, J = 3.5 Hz, Glc-H_1), 5.34 (1H, dd, J = 10.2 Hz, 3.5 Hz, Glc-H_2)), 5.53 (1H, s), 5.79 (1H, dd, J = 10.2 Hz, 9.8 Hz, Glc-H_3), 7.26–7.53 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 10.5, 13.2, 13.5, 13.6, 55.5, 63.7, 67.5, 68.6, 69.0, 69.6, 70.7, 75.2, 75.3, 76.1, 78.8, 79.2, 87.3, 88.0, 89.4, 90.7, 99.1, 101.7, 1264.4, 128.2, 128.3, 129.1, 137.0, 170.5, 173.2; IR (KBr) 2922, 1714, 1404, 1212, 1066, 759 cm^{-1}. Anal. calcd. for $C_{30}H_{32}FeO_8$: C, 62.51; H, 5.60. Found: C, 62.51; H, 5.42. Results of HPLC analysis (CrestPak C18S, hexane:ethyl acetate (12:1), 1.0 ml/min): t_R 29.1 **3ba**, and **3bb**, t_R 31.3 **3bc**. Compound **3ba** was subjected to a methanolysis reaction to afford (+)-2,2′,4,4′-tetramethylferrocen-1,1′-dicarboxylic acid methyl ester **5b** in 87% yield by the same procedure described before.

4.10. (+)-2,2′,4,4′-Tetramethylferrocen-1,1′-dicarboxylic acid methyl ester **5b**

$[\alpha]_D^{24} = +7.3$ (c 0.47, $CHCl_3$); M.p. $> 200^\circ C$ (decomposed), recrystallized from ether and hexane; R_f 0.35, hexane:ethyl acetate = 4:1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.88 (6H, s), 2.11 (6H, s), 3.78 (6H, s), 3.95 (3H, d, J = 1.3 Hz), 4.36 (2H, d, J = 1.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) 12.7, 13.0, 51.1, 72.4, 77.3, 86.3, 87.5, 171.6; IR (KBr) 2951, 1712, 1444, 1223, 1075, 778 cm^{-1}. Anal. calcd. for $C_{18}H_{22}FeO_4$: C, 60.35; H, 6.19. Found: C, 59.93; H, 6.37.

4.11. 4,6-O-Benzylidene-2,3-{(S*,S*)-(2,2′,4,4′-tetramethylferrocene-1,1′-dicarbonyl}-O-methyl-α-D-glucopyranoside **3bb**

$[\alpha]_D^{22} = +195$ (c 0.78, $CHCl_3$); R_f 0.46, hexane:ethyl acetate = 4:1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.89 (3H, s), 1.98 (3H, s), 2.05 (3H, s), 2.23 (3H, s), 3.46 (3H, s), 3.75–3.90 (3H, m, Glc-$H_{6\text{-axial}}$ and Fc-H), 4.02 (3H, dt, J = 9.7, 4.3 Hz, Glc-H_5), 4.13 (1H, s, Fc-H), 4.33 (1H, dd, J = 9.9, 4.3 Hz, Glc-H_4), 4.67 (1H, s, Fc-H), 4.88 (1H, d, J = 3.5 Hz, Glc-H_1), 5.28 (1H, dd, J = 10.2, 3.5 Hz, Glc-H_2), 5.56 (1H, s), 5.85 (1H, dd, J = 10.2, 9.9 Hz, Glc-H_3), 7.32-7.52 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 10.9, 13.3, 13.5, 13.6, 55.4, 63.6, 68.5, 68.8, 69.0, 69.1, 70.4, 76.0, 76.1, 78.6, 79.3, 87.0, 87.1, 89.7, 90.3, 99.2, 101.6, 126.3, 128.2, 128.3, 129.1, 136.9, 171.1, 172.7; IR (KBr) 2912, 1712, 1409, 1211, 1067 cm^{-1}. Methanolysis of this compound gave (–)-**5b** in quantitative yield: $[\alpha]_D^{24} = -5.1$ (c 0.43, $CHCl_3$). The IR and ^1H NMR are identical to the spectral data for (+)-**5b**. We assume that (+)-**5b** can be assigned to be (*R*,*R*) and (–)-**5b** to be (*S*,*S*) according to the specific rotation value of (*R*,*R*)-(+)-**5a.** We assume that both (+)-**5b** and (–)-**5b** possess at least more than 90% ee, because we could not detect any other isomer in both ^1H NMR spectra of (+)-**3ba** and (+)-**3bb**, while optical rotation values of (+)-**5b**, which was derived from (+)-**3ba**, was not in accord with that of (+)-**5b** which was derived from (+)-**3bb**.

4.12. 4,6-O-Benzylidene-2,3-{(R*,S*)-(2,2′,4,4′-tetramethylferrocene-1,1′-dicarbonyl}-O-methyl-α-D-glucopyranoside **3bc**

$[\alpha]_D^{22} = +303$ (c 0.66, $CHCl_3$); R_f 0.46, hexane:ethyl acetate = 4:1; ^1H NMR (200 MHz, $CDCl_3$) δ 1.90 (3H, s), 1.92 (3H, s), 2.18 (3H, s), 2.34 (3H, s), 3.46 (3H, s), 3.74–3.89 (2H, m, Glc-H_{6a}, H_{6b}), 3.96–4.05 (3H, m, Glc-H_5, Fc-H_5, Fc-H_5), 4.33 (1H, dd, J = 8.9 Hz, 4.4 Hz, Glc-H_4 eq), 4.34 (1H, brs, Fc-H_3), 4.46 (1H, brs, Fc-H_3), 4.88 (1H, d, J = 3.6 Hz, Glc-H_1), 5.29 (1H, dd, J = 10.2, 3.6 Hz, Glc-H_2), 5.54 (1H, s), 5.81 (1H, dd, J = 10.2, 10.0 Hz, Glc-H_3), 7.15-7.51 (5H, m); ^{13}C NMR (50 MHz, $CDCl_3$) 12.4, 12.5, 12.8, 55.4, 63.6, 68.5, 69.0, 70.5, 74.5, 74.7, 76.7, 77.6, 79.2, 88.7, 89.1, 89.6, 90.2, 99.2, 101.7, 125.3, 126.4, 128.2, 129.0, 136.9, 172.1, 172.8; IR (KBr) 2958, 1715, 1413, 1068 cm^{-1}. We are assuming that glucoside ester **3bc** possesses the (*R*,*S* or *S*,*R*)-ferrocenyl part because ester **5b** which was obtained by the methanolysis of **3bc** showed no specific rotation.

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References

1. For recent reviews, see: (a) Hudson, S. A.; Maitlis, P. M. *Chem. Rev.* **1993**, *93*, 861. (b) Miller, J. S.; Epstein, A. J.; Reiff, W. M. *Acc. Chem. Res.* **1988**, *21*, 114. (c) Sawamura, M.; Ito, Y. *Chem. Rev.* **1992**, *92*, 857. (d) Togni, A. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1475. For a review of biologically active iron-containing sandwich compounds: Köpf-Maier, P.; Köpf, H. *Chem. Rev.* **1987**, *87,* 1137.
2. For examples of biologically active ferrocenes, see: (a) Köpf-Maier, P.; Köpf, H.; Neuse, E. W. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 456. (b) Murray, J. H.; Harding, M. M. *J. Med. Chem.* **1984**, *37*, 1936. (c) Klimova, Ye. I.; Postnov, V. N.; Meleshonkova, N. N.; Garcia, M. Martines; Zaks, A. S.; Yushkov, V. V. *Khim.-Farm. Zh.* **1994**, *28*, 30. (d) Garcîa, M. M.; Pérez, G. E.; Ochoa, F. L.; Cruz-Almanza, R. *Tetrahedron* **1997**, *53*, 12369. (e) Tamura, H.; Miwa, M. *Chem. Lett.* **1997**, 1177. (f) Bucci, E.; De Napoli, L.; Du Fabio, G.; Messere, A.; Montesarchio, D.; Romanelli, A.; Piccialli, G.; Varra, M. *Tetrahedron* **1999**, *55*, 14435, (g) Itoh, T.; Shirakami, S.; Ishida, N.; Yamashita, Y.; Yoshida, T.; Kim, H.-S.; Wataya, Y. *Bioorg. Med. Chem. Lett.* **2000**, *10*, in press, and references cited therein.
3. (a) Sawamura, M.; Hamashima, H.; Ito, Y. *Tetrahedron: Asymmetry* **1991**, *2*, 593. (b) Kuwano, R.; Sawamura, M.; Okuda, S.; Asai, T.; Ito, Y.; Redon, M.; Krief, A. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 2807, and references cited therein.
4. Uno, M.; Ando, K.; Komatsuzaki, N.; Takahashi, S. *J. Chem. Soc., Chem. Commun.* **1992**, 964.
5. (a) Itoh, T.; Chika, J.-I. *J. Org. Chem.* **1995**, *60*, 4968. (b) Itoh, T.; Chika, J.-I.; Shirakami, S.; Ito, H.; Yoshida, T.; Kubo, Y.; Uenishi, J.-I. *J. Org. Chem.* **1996**, *61*, 3700. (c) Itoh, T.; Shirakami, S.; Nakao, Y.; Yoshida, T. *Chem. Lett.* **1998**, 979.
6. Racemic (±)-**1b** was prepared by the reaction of 2,4-dimethylcyclopenta-1,3-diene-1-carboxylic acid [13] with $FeCl_2$ according to Ref. 4.
7. Nelson, T. D.; Meyers, A. I. *J. Org. Chem.* **1994**, *59*, 2577.
8. In addition, due to the low solubility of the acid **4a**, it was difficult to obtain the specific rotation value of **4a** with sufficient reliability.
9. Roush, W. R.; Reilly, M. L.; Koyama, K.; Brown, B. B. *J. Org. Chem.* **1997**, *62*, 8708.
10. MacSpartan Plus was employed for the MO (PM3 level) calculation for **5a**.
11. For the CD exciton theory see: Harada, N.; Nakanishi, K. *Circular Dichroic Spectroscopy–Exciton Coupling in Organic Stereochemistry*; University Science Books: Mill Valley, CA, and Oxford University Press: Oxford, 1983.
12. Crystallographic data have been deposited with the Cambridge Crystallographic Centre, Cambridge, UK.
13. Hatanaka, M.; Himeda, Y.; Ueda, I. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2269.