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Ferrocene–Carbohydrate Conjugates as Electrochemical Probes for Molecular Recognition Studies

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Abstract: We report two methods that have allowed the attachment of glucose, mannose and lactose to one or both of the cyclopentadienyl rings of ferrocene. The resulting ferrocene–carbohydrate conjugates were synthesised by the reaction of thioglycosides with ferrocenemethanol and 1,1′-ferrocenedimethanol in acidic media. A second method based on the regiospecific copper(I)-catalysed cycloaddition of propargyl glycoside, azidomethyl and bis(azidomethyl)ferrocene as well as azidoethyl glycoside and ethynylferrocene was also used and led to the synthesis of 1,2,3-triazole-containing glycoconjugates. The electrochemical behaviour of the synthesised glycoconjugates was investigated. In addition, their binding interactions with β-cyclodextrin were studied by means of NMR spectroscopy, isothermal titration calorimetry, and cyclic and differential pulse voltammetric experiments. These techniques allowed the determination of the thermodynamic parameters of the complexes, the stability constants for the complexes formed with both the neutral and the oxidised states of the ferrocenyl glycoconjugates, the mode of inclusion and the diffusion coefficients for both the glycoconjugates and the complexes.

Keywords: click chemistry · ferrocene · glycoconjugates · molecular sensors · voltammetry

Introduction

The understanding of the molecular recognition phenomena that involve carbohydrates and cell-surface proteins interactions is crucial for the elucidation of many key biological events, such as viral and bacterial infections, cell–cell adhesion, inflammatory and immune response, fertilisation and cancer metastasis.[1] The study of such interactions is the main aim of glycomics, which pursues the understanding of the role of carbohydrates in biological systems. Other directly or indirectly related research areas, such as the design of diagnostic and therapeutic agents, should also benefit from these studies. It has been acknowledged that advances in this field involve the indispensable development of synthetic tools that can be used for correlating structure and function, to inhibit, modulate, detect and probe those interactions.[2] In this respect, most of the carbohydrate–protein interaction detection methods are based on labelled proteins or carbohydrates with a fluorescent or a biotin moiety, so that the recognition event induces a measurable signal.[3] There are very few cases of biosensors based on carbohydrates labelled with electroactive moieties that trigger electrochemical signals upon binding with the complementary supramolecular partner, such as a lectin.[4] Electrochemical biosensors possess the advantages of low cost and high sensitivity with relatively simple instrumentation, they are more susceptible to miniaturisation and well suited for operating in turbid media.[5] On the other hand, ferrocene-containing compounds bearing molecular recognition binding sites have received wide attention in recent years due to the possibility

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of building redox-switching or sensing systems of a molecular or supramolecular nature, which can be controlled through the application of external stimuli.[6] In this regard, ferrocene-containing carbohydrates could be of particular interest as their reversible and tunable redox properties could be applied for the development of biosensors for the detection of carbohydrate–protein interactions, as well as for the development of devices that allow a redox switchable and tunable control of such interactions. Furthermore, it is known that many lectins, in addition to the carbohydrate binding sites, possess hydrophobic binding sites, in particular around the site at which aglycon would localise upon carbohydrate–lectin complexation.[7] Thus, in many cases, aryl glycosides form more stable complexes with lectins than their analogues, which do not have hydrophobic substituents, indicating either that the binding pocket itself is hydrophobic or additional hydrophobic sites exist close to the primary carbohydrate binding site. Ferrocene is a small-size molecule of hydrophobic nature that undergoes a fast and reversible one-electron oxidation to give ferrocenium ion at readily accessible redox potentials.[6] Taking into account those facts, one would think that ferrocene, when situated at aglycon site of the saccharide, would be involved in the lectin binding interaction, while its oxidation would lead to a dramatic diminishing of the stability of the lectin–carbohydrate complex.

A number of methods for the conjugation between the carbohydrate and the ferrocene moieties have been reported.[6e,8,9] Most of these conjugates are obtained by *O*-, *S*- and *N*-acylation of carbohydrates with 1-ferrocenecarbonyl chloride and 1,1′-ferrocene dicarbonyl chloride.[6e,8b–f] Other methods involve *O*- and *C*-glycosidation,[6e,8e,g] and ferrocenylalkylations.[6e,8a]

Herein, we report the results obtained after exploring efficient and versatile methods to provide an easy access to ferrocene–carbohydrate conjugates.[9] Two synthetic strategies have been developed giving rise to ferrocenyl carbohydrates with tethers of different length and chemical nature. To evaluate the potential of these ferrocenyl glycoconjugates as redox probes, we studied their electrochemical properties and their guest binding properties toward β-cyclodextrin. Cyclodextrins, in addition to having been shown to be useful as models to understand noncovalent binding interactions of carbohydrates in water,[10] form inclusion complexes with ferrocene derivatives in their neutral state.[11]

Results and Discussion

Synthesis: The electrophilic reactivity of the 1-ferrocenylmethyl position[12] allows an easy alkylthiolation of that position by direct reaction between the alkylthiol and hydroxymethylferrocene in acidic media.[13] The treatment of 1-hydroxymethylferrocene (**1**) and the glycosyl thiols **2–4** with TFA in anhydrous CH_2Cl_2 at room temperature led to the ferrocenylmethyl–thioglucopyranoside, –thiomannopyranoside, and –thiolactoside **5–7** in 90–94% yields (Scheme 1). We also prepared the divalent glycosyl–ferrocene derivatives by reaction of the glycosyl thiols **2–4** with 1,1′-bis-(hydroxymethyl)ferrocene (**8**) under similar conditions. The bis-(glycosyl)–ferrocene derivatives **9–11** were isolated after column chromatography in good yields (87–92%). Removal of the acetyl groups of **5–7** and **9–11** with NaOMe afforded the monovalent and divalent ferrocene–carbohydrate conjugates **12–17** with a methylenethio tether.

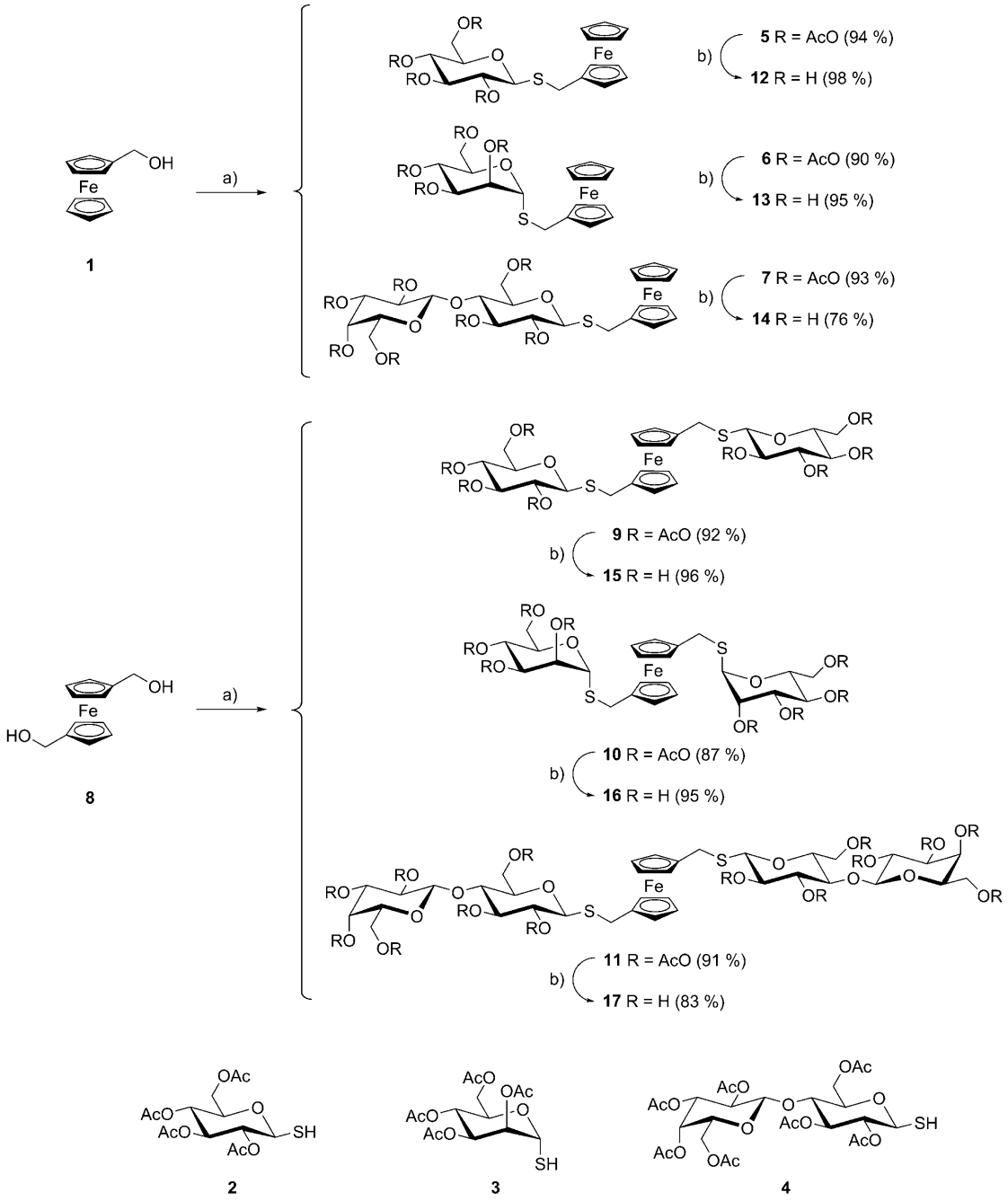
The second strategy was based on the application of "click chemistry" and involved the Cu^I-catalysed 1,3-dipolar cycloaddition reaction between a terminal alkyne and an azide. This reaction, which leads only to the 1,4-disubstituted 1,2,3-triazole, has demonstrated to be an extraordinarily efficient method for the construction of bioconjugates.[14,15]

Treatment of ferrocenes **1** and **8** with sodium azide in acetic acid efficiently gave the corresponding azido derivatives **18** and **19** in 92 and 93% yield, respectively. We used these compounds to investigate the regiospecific coupling with alkyne derivatives of carbohydrates. Thus, the reaction of propargyl glycosides **20–22** with azido ferrocenes **18** and **19** in toluene under reflux with catalytic amounts of $(EtO)_3P{\cdot}CuI$ afforded after 45 min and column chromatography the mono- and diglycosylated 1,2,3-triazoles **23–28** in 88–99% yields (Scheme 2). The same reaction conditions were used for the coupling of the 2-azidoethyl glycosides **30** and **31** and 1-ethynylferrocene **29** leading to the corresponding monoglycosylated 1,2,3-triazoles **32** and **33** in 95 and 98% yield, respectively.

We also performed some reactions in protic solvents. The coupling of glucoside **30** with 1-ethynylferrocene **29** with the same catalyst but in methanol under reflux gave the 1,2,3-triazole **32** in 59% yield, after 2 h of reaction time. However, the reaction of the propargyl glucoside derivative **20** with 1-(azidomethyl)ferrocene **18** under the same conditions did not lead to the expected 1,2,3-triazole but to 1-(methoxymethyl)ferrocene, as a result of the substitution of the azido group by methanol. Finally, de-*O*-acetylation of compounds **23–28**, **32** and **33** by treatment with NaOMe gave the 1,2,3-triazole-tethered ferrocene–carbohydrate conjugates **34–41** in 88–97% yields with a saccharide group attached to one or both cyclopentadienyl rings of the metallocene.[16]

Electrochemical behaviour: The electrochemical properties of ferrocene–carbohydrate conjugates **12–17** and **34–41** can be studied by cyclic voltammetry (CV) and differential pulse voltammetry (DPV).[16] Thus, their cyclic voltammograms showed reversible redox couples of ferrocene/ferrocenium (see Figure 1 and Supporting Information). The values of the half-wave potential ($E_{1/2}$) for the oxidation of the ferrocene core and the diffusion coefficient (D_f) are shown in Table 1. The DPV voltammograms of conjugates **12–17**, **34–38**, **40** and **41** reveal only one oxidation peak for each ferrocene derivative, meaning that in aqueous solution the conjugates are present in only one electroactive distinguishable form.

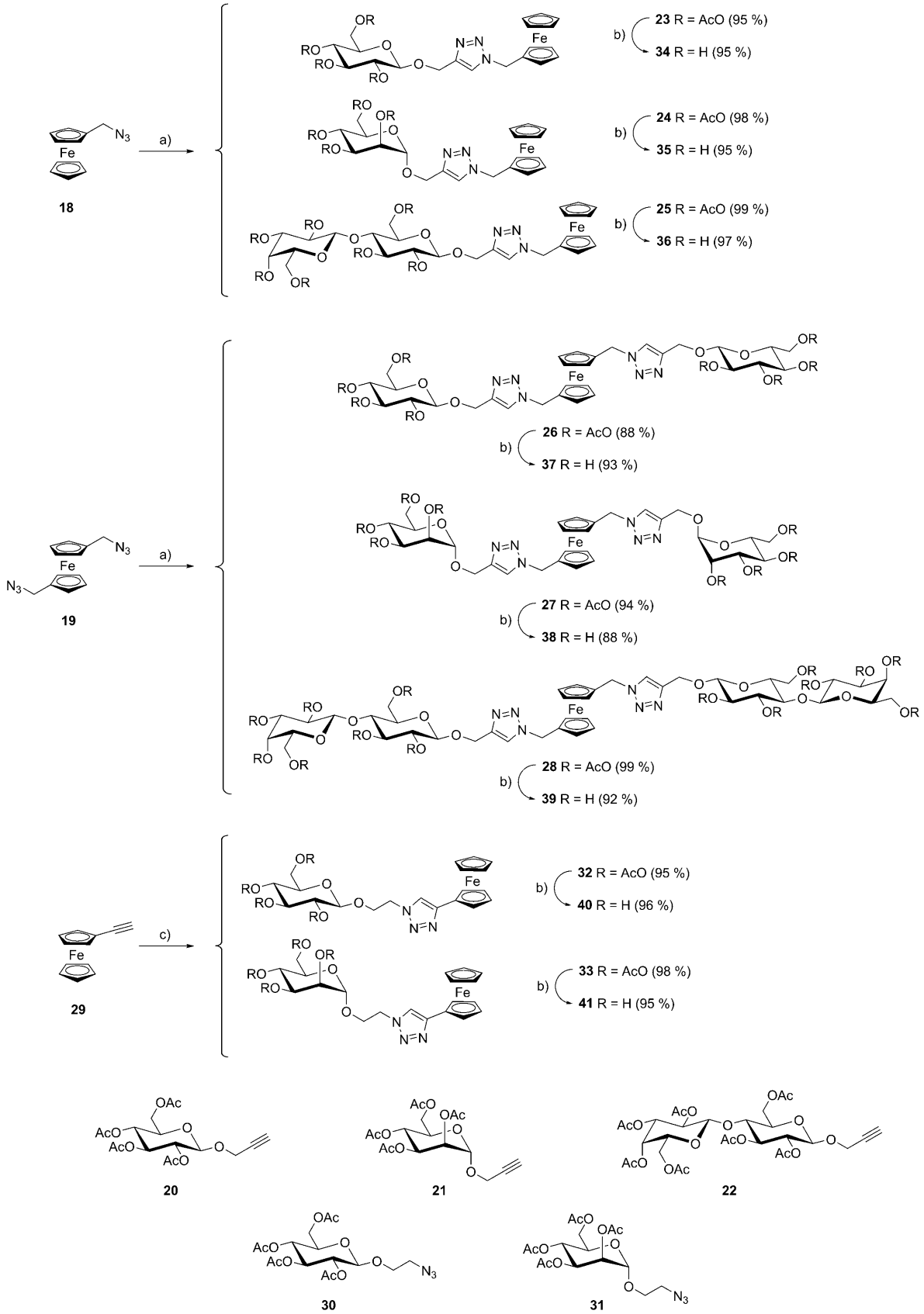
As illustrated in Table 1, the carbohydrate moiety barely influences the $E_{1/2}$, since no significant differences are ob-



Scheme 1. Synthesis of thioglycosylated ferrocenes. Reagents and conditions: a) **2**, **3** or **4**, TFA, CH_2Cl_2, RT, 2 h; b) NaOMe, MeOH, RT, 2–20 h.

served for conjugates with the same tether and ferrocene cores but different carbohydrates. However, the $E_{1/2}$ value of the ferrocene core increases on moving from the CH_2S tether to the CH_2-1,2,3-triazole-CH_2O tether, in concordance with the electron-acceptor nature of the substituent.[17] A slight decrease of $E_{1/2}$ is observed when the CH_2-1,2,3-triazole-CH_2O tether is substituted by the 1,2,3-triazole-CH_2CH_2O tether, possibly owing to some conjugation effect of ferrocenyl group with the triazole ring in the oxidation products.[18] Also, the $E_{1/2}$ increases from the monoglycosylated ferrocenes to those that are diglycosylated. These effects can be attributed to the different degrees of shielding of the ferrocene core by the glycosyl-tether branches preventing solvent interactions, such that the ferrocenium ion resulting from the oxidation process is less stabilised by the solvent shielding.[19]

The D_f values listed in Table 1 are consistent with the degree of substitution of the ferrocene. According to the Stokes–Einstein equation, the D_f parameter is inversely proportional to the hydrodynamic radius of the molecule. Therefore, a higher molecular mass of the glycoconjugate is expected to diffuse more slowly. Nevertheless, there are



Scheme 2. Synthesis of 1,2,3-triazole derivatives. Reagents and conditions: a) **20**, **21** or **22**, $(EtO)_3P{\cdot}CuI$, toluene, reflux, 45 min; b) NaOMe, MeOH, RT, 2–20 h; c) **30** or **31**, $(EtO)_3P{\cdot}CuI$, toluene, reflux, 45 min.

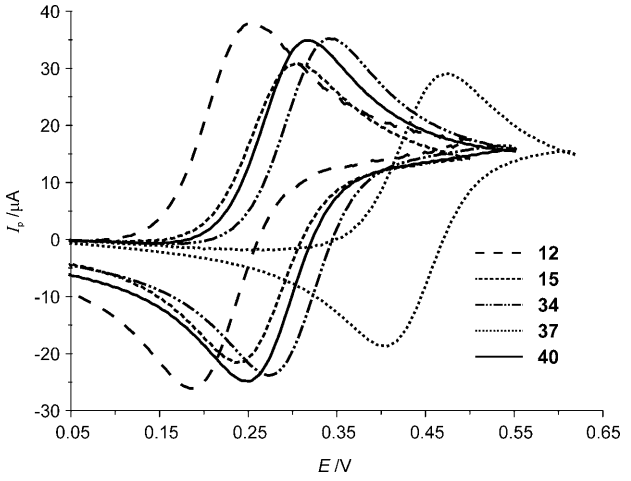


Figure 1. Cyclic voltammetry curves (5 scans, sweep rate = 0.1 V s^{-1}) of the glycosyl conjugates **12**, **15**, **34**, **37** and **40** (0.5 mM) in 50 mM NaCl aqueous solution at 21 °C. These experiments illustrate the effect of the tether and the substitution grade on the half-wave potential ($E_{1/2}$) of the ferrocene units.

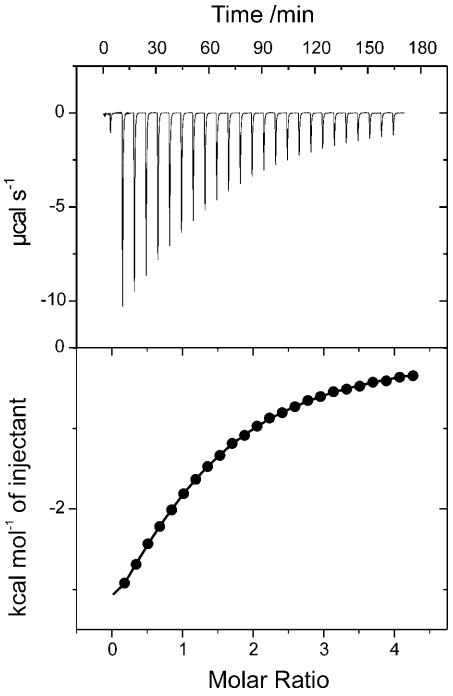


Figure 2. Titration of divalent mannoside-containing conjugate **38** (0.54 mM) with 25 aliquots (10 μL each) of β-CD (stock concentration of 12.13 mM) in 20 mM phosphate buffer (pH 7.0) with 20 mM NaCl at 25 °C. The top panel shows the raw calorimetric data, denoting the amount of generated heat (negative exothermic peaks) following each injection of the macrocycle. The area under each peak represents the amount of heat released upon the binding of conjugate **38** to β-CD. Note that, as the titration progresses, the area under the peaks gradually becomes smaller due to an increased complexation of the guest by β-CD. This area was integrated and plotted against the molar ratio of β-CD to **38** (bottom panel). The smooth solid line represents the best fit of the experimental data to a model of *n* equal and independent sites.

some compounds, such as **15**, **16**, **34** and **35**, that show very different D_f values despite their stereoisomeric relationships. These results can be accounted for by different molecular-level friction effects[20] in which the spatial orientation of the functional groups involved and the different stereochemistry-dependent hydration modes of carbohydrates[21] could play a key role.

Binding interactions with β-CD: The guest binding ability of carbohydrate–ferrocene conjugates **12**–**17**, **34**–**38**, **40** and **41** towards β-cyclodextrin was studied by employing isothermal titration calorimetry (ITC) and voltammetric methods. In ITC experiments, stepwise addition of aliquots of a solution of β-CD to a guest-containing solution led to a decrease in the extent of released heat as shown by a typical illustration of the thermogram and isotherm (Figure 2). These experiments were performed in pH 7.0 phosphate buffer at 25 °C. ITC data can be fit by using a nonlinear least-square algorithm with three independent variables (namely *n*, ΔH, and *K*) for the simplest model based on equal and independent

Table 1. Half-wave potentials ($E_{1/2}$) and diffusion coefficients in the absence (D_f) and in the presence (D_c) of β-CD by cyclic voltammetry for glycoconjugates **12**–**17**, **34**–**38**, **40** and **41** in aqueous solution with 50 mM NaCl as supporting electrolyte at 21 °C.

Glycoconjugate	$E_{1/2}$[a] [V]	D_f[b] $\times 10^6$ [cm^{2}s^{-1}]	D_f[c] $\times 10^6$ [cm^{2}s^{-1}]	D_c[c] $\times 10^6$ [cm^{2}s^{-1}]	D_c/D_f[d]
12 [Fc(CH$_2$SGlc)]	+0.221	5.3 ± 0.4	5.48 ± 0.14	2.38 ± 0.15	0.45 ± 0.06
13 [Fc(CH$_2$SMan)]	+0.226	5.2 ± 0.4	5.46 ± 0.13	2.51 ± 0.12	0.48 ± 0.06
14 [Fc(CH$_2$SLac)]	+0.224	3.5 ± 0.2	3.86 ± 0.12	1.29 ± 0.11	0.37 ± 0.05
15 [Fc(CH$_2$SGlc)$_2$]	+0.270	3.5 ± 0.3	3.70 ± 0.04	1.98 ± 0.06	0.57 ± 0.07
16 [Fc(CH$_2$SMan)$_2$]	+0.274	2.7 ± 0.2	3.86 ± 0.07	2.24 ± 0.07	0.84 ± 0.08
17 [Fc(CH$_2$SLac)$_2$]	+0.273	2.9 ± 0.2	–[e]	–[e]	–[e]
34 [Fc(CH$_2$TACH$_2$Glc)]	+0.307	4.7 ± 0.2	4.73 ± 0.03	2.04 ± 0.04	0.44 ± 0.03
35 [Fc(CH$_2$TACH$_2$Man)]	+0.313	5.3 ± 0.3	5.64 ± 0.11	3.10 ± 0.14	0.58 ± 0.06
36 [Fc(CH$_2$TACH$_2$Lac)]	+0.308	5.9 ± 0.6	6.0 ± 0.2	3.7 ± 0.2	0.63 ± 0.10
37 [Fc(CH$_2$TACH$_2$Glc)$_2$]	+0.430	3.4 ± 0.2	3.02 ± 0.03	1.44 ± 0.07	0.42 ± 0.05
38 [Fc(CH$_2$TACH$_2$Man)$_2$]	+0.445	3.3 ± 0.4	3.35 ± 0.08	1.1 ± 0.2	0.33 ± 0.07
40 [Fc(TACH$_2$CH$_2$Glc)]	+0.283	4.6 ± 0.3	4.86 ± 0.05	2.32 ± 0.06	0.50 ± 0.05
41 [Fc(TACH$_2$CH$_2$Man)]	+0.289	4.7 ± 0.2	5.31 ± 0.09	2.67 ± 0.10	0.57 ± 0.05

[a] Calculated as $E_{1/2} = (E_{pa} + E_{pc})/2$. [b] Calculated from the Randles–Ševčik equation [Eq. (2)]. [c] Calculated from Equation (5). [d] Calculated using D_f values obtained from the Randles–Ševčik equation [Eq. (2)]; see reference [29]. [e] CV experiments for this compound were not measured due to its complex behaviour in the presence of β-CD.

Table 2. Thermodynamic data and stability constants for the binding of neutral (K) and oxidised (K_{Ox}) forms of guests **1**, **12–17**, **34–38**, **40** and **41** to β-CD obtained from calorimetric and voltammetric experiments.

Guest	Calorimetry[a]				Voltammetry[b]	
	$K\times10^{-3}$ [M^{-1}]	$-\Delta G^0$ [kcal mol^{-1}]	$-\Delta H$ [kcal mol^{-1}]	$T\Delta S^0$ [kcal mol^{-1}]	$K\times10^{-3}$ [M^{-1}]	K_{Ox} [M^{-1}]
1 [Fc(CH_2OH)][c]	10.0	5.4	6.1	−0.7	–	–
12 [Fc(CH_2SGlc)]	9.9 ± 0.3	5.45 ± 0.02	5.90 ± 0.07	-0.45 ± 0.07	10.1 ± 0.2	208 ± 5
13 [Fc(CH_2SMan)]	16.1 ± 0.9	5.74 ± 0.03	5.96 ± 0.08	-0.22 ± 0.09	16.3 ± 0.3	218 ± 6
14 [Fc(CH_2SLac)]	9.1 ± 0.4	5.40 ± 0.03	6.99 ± 0.10	-1.59 ± 0.10	15.1 ± 0.2	211 ± 5
15 [Fc($CH_2SGlc)_2$]	2.2 ± 0.1	4.55 ± 0.01	6.26 ± 0.10	-1.71 ± 0.10	2.7 ± 0.1	203 ± 5
16 [Fc($CH_2SMan)_2$]	5.7 ± 0.4	5.12 ± 0.04	7.44 ± 0.23	-2.32 ± 0.23	11. 9 ± 0.5	170 ± 18
17 [Fc($CH_2SLac)_2$]	3.6 ± 0.1	4.85 ± 0.02	6.50 ± 0.11	-1.65 ± 0.11	1.1 ± 0.1[d]	179 ± 7[d]
34 [Fc(CH_2TACH_2Glc)]	5.2 ± 0.1	5.07 ± 0.01	5.66 ± 0.07	-0.59 ± 0.07	5.8 ± 0.1	224 ± 6
35 [Fc(CH_2TACH_2Man)]	5.5 ± 0.4	5.10 ± 0.04	5.48 ± 0.15	-0.38 ± 0.15	5.5 ± 0.1	218 ± 5
36 [Fc(CH_2TACH_2Lac)]	5.0 ± 0.1	5.05 ± 0.01	5.83 ± 0.05	-0.78 ± 0.05	5.9 ± 0.1	207 ± 5
37 [Fc($CH_2TACH_2Glc)_2$]	1.6 ± 0.1	4.37 ± 0.01	6.15 ± 0.10	-1.78 ± 0.10	1.9 ± 0.1	179 ± 6
38 [Fc($CH_2TACH_2Man)_2$]	1.6 ± 0.1	4.36 ± 0.01	6.37 ± 0.10	-2.01 ± 0.10	1.9 ± 0.1	200 ± 5
40 [Fc($TACH_2CH_2Glc$)]	6.7 ± 0.1	5.22 ± 0.01	6.05 ± 0.03	-0.83 ± 0.03	7.1 ± 0.1	200 ± 4
41 [Fc($TACH_2CH_2Man$)]	6.4 ± 0.7	5.19 ± 0.07	5.96 ± 0.23	-0.77 ± 0.24	7.0 ± 0.1	200 ± 5

[a] Determined in 20 mM phosphate buffer (pH 7.0) with 20 mM NaCl. [b] Determined in aqueous solutions with 50 mM NaCl. [c] Reference [22e]. [d] Data obtained from DPV.

binding sites. The analysis of the ITC data using that model yielded n values from 0.81 to 1.36, consistent with a 1:1 stoichiometry of binding for both cases, mono- and disubstituted ferrocenes, in accordance with the most commonly claimed stoichiometry ratio for ferrocene/β-CD complexes.[11,22] As can be seen from Table 2 and Figure 3, all the ferrocene glycoconjugate/β-CD complexes formation are exothermic

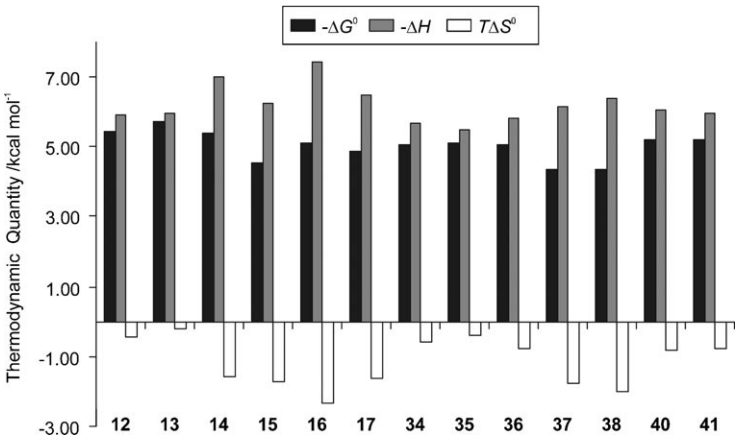


Figure 3. Free-energy ($-\Delta G^0$), enthalpy ($-\Delta H$), and entropy changes ($T\Delta S^0$) for the inclusion complexation of ferrocene-containing glycoconjugates **12–17**, **34–38**, **40** and **41** with β-cyclodextrin in 20 mM phosphate buffer (pH 7.0) with 20 mM NaCl at 25 °C.

and enthalpy-driven with an unfavourable entropic term ($T\Delta S<0$). The equilibrium constants (K) for the binding interactions of ferrocene–carbohydrate conjugates with β-CD are within the same order of magnitude ($10^3\,M^{-1}$) as other ferrocene derivatives,[22] with the exception of the thiomannosyl–ferrocene derivative **13**, which has a K value of $1.61\times10^4\,M^{-1}$. Considering that the estimated K value for the complex ferrocene/β-CD is $3.5\times10^3\,M^{-1}$ (measured by voltammetry in a 95:5 H_2O/CH_3CN mixture),[22d] the presence of the carbohydrate moiety and the tether attached to the ferrocene molecule affords inclusion complexes with slightly higher or lower stability. A similar behaviour has been reported for complexes formed between 1-adamantylmethyl and *p*-nitrophenyl glycosides and cyclodextrins (α and/or β).[10b,23] In our case, monosubstituted ferrocene derivatives **12–14**, **34–36**, **40** and **41** form more stable complexes than ferrocene, with a K value higher than $5\times10^3\,M^{-1}$. Examination of Table 2 and Figure 3 show that the thermodynamic profiles of these monosubstituted ferrocene derivatives, with the exception of **14**, are very similar to that of ferrocenemethanol (**1**),[22e] that is, favourable ΔH values between −5.48 and −6.05 kcal mol^{-1} and entropic loss of about 3 to 14% with respect to the enthalpic term. These data suggest that the inclusion complexation mode of monosubstituted derivatives **12–13**, **34–36**, **40** and **41**, and ferrocenemethanol are very similar; the ferrocene moiety fits into the CD cavity in an axial mode, while the substituent protrudes out. A two-dimensional ROESY experiment with an equimolar mixture of β-CD and compound **12** was carried out to further support the proposed inclusion mode (Figure 4). This spectrum shows intermolecular NOE cross-peaks between the protons of the unsubstituted cyclopentadienyl ring of the ferrocene moiety and both the H-3 and H-5 protons on the interior wall of the cyclodextrin. In addition, there is a cross-peak between the substituted ferrocene cyclopentadienyl ring protons and H-3 of the cavity, but we did not find any NOE signals between those ferrocene protons and H-5 of CD. These results are consistent with an axial mode of inclusion of the ferrocene moiety into the CD cavity through the secondary face of the macrocycle.

As can be readily seen from Table 2, the highest K values are shown by the monosubstituted CH_2S-tethered ferrocenes **12–14**, in which the carbohydrate moiety is the closest to the ferrocene ring in the synthesised series. In the case of the triazole-containing monoglycosylated ferrocenes, those with the triazole directly bound to the ferrocene cyclopentadienyl ring, **40** and **41**, form more stable complexes with CD. By comparing guests that have the same tether but different

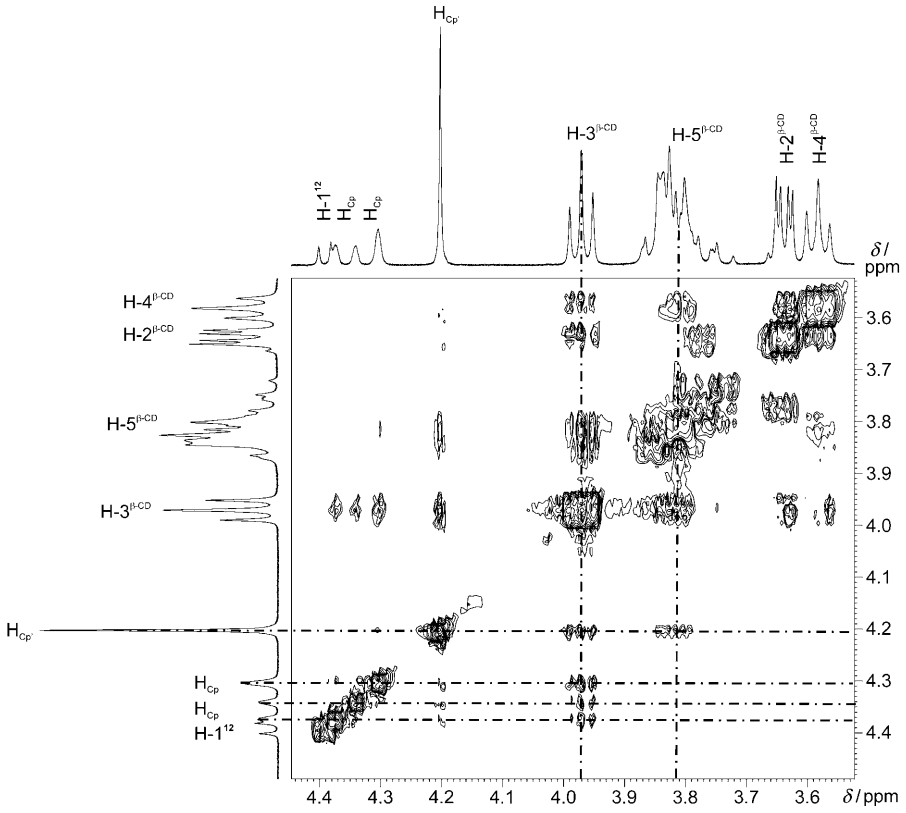


Figure 4. 2D-ROESY spectrum for a mixture of **12** (2 mM) and β-CD (2 mM) in D_2O at 25 °C with a mixing time of 200 ms.

carbohydrate moieties, we observe that mannose-containing ferrocenes **13** and **35** yield the most stable complexes, followed by glucose-containing ferrocenes **12** and **34**, and then lactose-containing ferrocenes **14** and **36**. In line with the results reported for the thermodynamics of α-CD/*p*-nitrophenyl glycosides complexes,[10b] those reported for β-CD/ferrocene–carbohydrate conjugates complexes show that the enthalpy of binding is provided mainly by the ferrocene moiety. The carbohydrate moiety, however, can modulate the thermodynamics of binding. This modulation effect has been associated with a hydration effect that would be governed by the stereochemistry of the carbohydrate,[10b] as proposed by Galema and Høiland.[21] In our case, for guests having the same tether but different carbohydrate moieties we observed a slight variation of their *K* values. This variation of the *K* values is particularly noticeable for those with a shorter tether.

The inclusion complexation of disubstituted ferrocene glycoconjugates **15**–**17** and **37**–**38** with β-CD is also exothermic and enthalpy-driven, although they afforded less stable complexes than the monosubstituted ferrocenes. Nevertheless, their thermodynamic profiles display an enthalpic gain higher than that shown by the monosubstituted analogues, along with a higher entropic loss. The results suggest that the structure of the disubstituted ferrocenes/β-CD complexes is different to that attributed to the complexes with monosubstituted ferrocenes. Thus, an equatorial orientation of the ferrocene moiety inside the CD cavity would provide a better size-matched guest cavity, and as a result a larger enthalpic gain is expected upon complexation due to the critical dependence of the van der Waals forces on the distance of separation.[24] On the other hand, for the penetration of the ferrocene moiety inside the CD cavity, the adoption of the cisoid conformation by the disubstituted conjugate is required, which would involve a more negative entropic term. To further investigate the structure of the complex, we measured a 2D-ROESY experiment of **15** in the presence of β-CD (Figure 5). The spectrum showed a set of cross-peaks between the protons H-3 and H-5 of CD and of both ferrocene cyclopentadienyl rings, supporting the proposed equatorial inclusion of the ferrocene core into the CD cavity with the two carbohydrate moieties sticking out. Likewise, a similar 2D-ROESY spectrum was found for the mixture of **14** and β-CD (see Supporting Information), suggesting for this case an equatorial mode of inclusion of the ferrocene moiety, unlike the rest of the monosubstituted derivatives, but in agreement with the thermodynamic profile of the β-CD/**14** complex, which was found to be similar to that of the disubstituted derivatives.

The effect of carbohydrate moieties on the complex stability depends on the nature of the tether. Thus, this effect is particularly relevant in the case of CH_2S-tethered conjugates **15**–**17**, in which the modulating role of the carbohydrate substituent is manifested by the different *K* values that were found to show an increasing value in the order **16** > **17** > **15**. By contrast, the influence of the carbohydrate substituents in the stability of the complexes with CH_2-1,2,3-triazole-CH_2-tethered conjugates is negligible, perhaps due to larger separation of the pendant carbohydrate from the macro cycle.

In light of results obtained from ITC experiments, we next studied the electrochemical behaviour of glycoconjugates **12**–**17**, **34**–**38**, **40** and **41** in the presence of β-CD. CV and DPV experiments were performed on Pt working electrodes at a scan rate of 0.10 $V s^{-1}$ and 0.01 $V s^{-1}$, respectively, in aqueous solutions of NaCl (50 mM) containing glycoconjugate (0.5 mM) and variable concentrations of β-CD (0–5 mM). The CV and DPV voltammograms (Figure 6 and Supporting Information) display progressive shifts of the

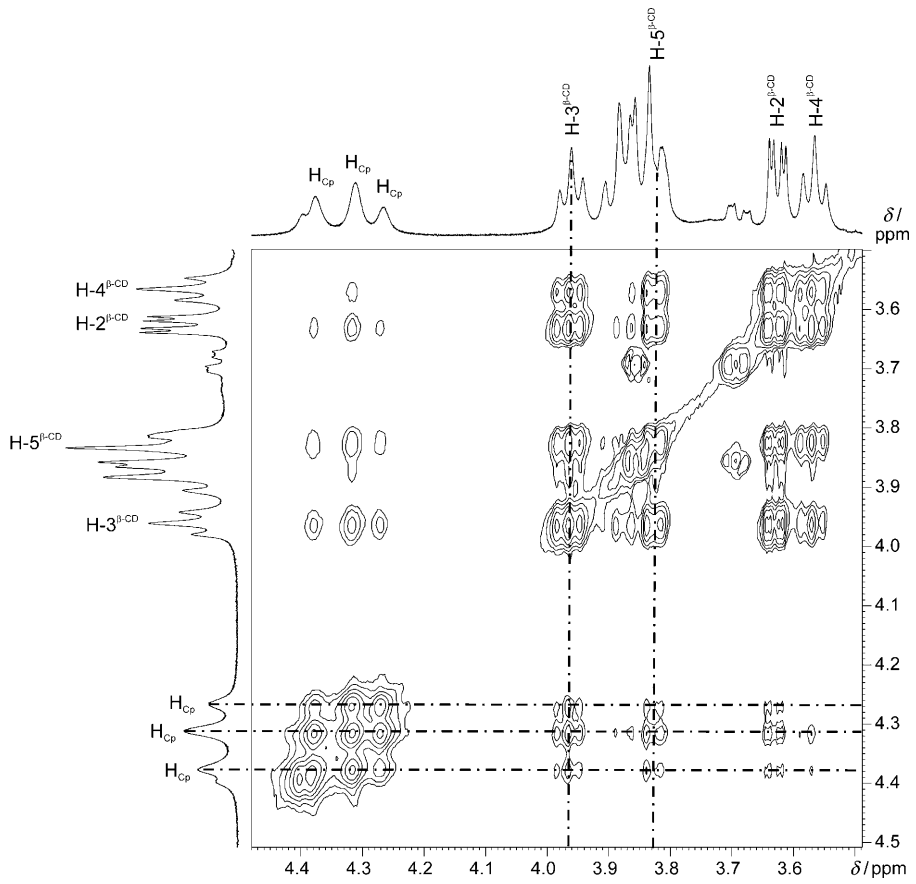


Figure 5. 2D-ROESY spectrum for a mixture of **15** (2 mM) and β-CD (2 mM) in D_2O at 25 °C with a mixing time of 200 ms.

half-wave potential for the ferrocene oxidation to more positive values with the increase of the β-CD concentration, while simultaneously the peak current gradually decreases. This voltammetric behaviour clearly corresponded to that expected from ferrocene-containing compounds.[11,22]

The analysis of the voltammetric results by using the method proposed by Mendoza et al.[25] allowed us to determine the stability constants for both the neutral form (K) and the oxidised form (K_{ox}) of the glycoconjugates. Accordingly, using the variation of the half-wave potential shift obtained from the CV with the concentration of β-CD (Figure 7) it was possible to calculate the K values outlined in Table 2. As can be seen, the K values obtained from voltammetry resulted in a good fit with those obtained from calorimetry, with the exception of conjugates **14** and **16**, which yielded K values approximately two fold higher than those obtained from calorimetry. We have not found a plausible explanation for that result. An estimation of the stability of the ferrocenium glycoconjugate cation/β-CD complexes can be obtained through Equation (1), in which $E^{c}_{1/2}$ and $E^{f}_{1/2}$ are the half-wave oxidation potential for the complexed and free forms of the ferrocene moiety, respectively.

$$E^{c}_{1/2} = E^{f}_{1/2} + \frac{RT}{nF}\ln\frac{K}{K_{ox}} \quad (1)$$

Thus, ferrocenium glycoconjugate cations afforded substantially less stable complexes with β-CD than the reduced counterparts, as expected. The K_{ox} values are in the range between 224 and 170 M^{-1}, in accordance with the weak interaction between the ferrocenium moiety and CD cavity. However, these K_{ox} values are slightly larger than those reported for simple ferrocene derivatives, often found in the order of magnitude of 1.[22d,26]

The decrease of the peak currents (see Figure 6) as the host concentration increases is the result of the decrease of the diffusion coefficients of the electroactive species upon complex formation: the higher the hydrodynamic radius of diffusing species, the lower the diffusion coefficients. The relation of the anodic peak current for the guest in a cyclic voltammogram at any given concentration of the host and the apparent diffusion coefficient (D_{app}) of the reduced form of the guest is defined through the Randles–Ševčik equation [Eq. (2)],[25,27] in which I_p is the anodic peak current, n is the number of electrons transferred in the process, A is the electrode area, C_0 is the concentration of the electroactive species and ν is the scan rate.

$$I_p = 0.4463\left(\frac{F^3}{RT}\right)^{1/2} n^{3/2} A C_0 (D_{app}\nu)^{1/2} \quad (2)$$

The relation between the D_{app} values and the mole fraction of the free guest (χ_f) is expressed by the Equation (3), in which D_f and D_c are the diffusion coefficients of the free and complexed forms of the electroactive guest, respectively, and χ_f can be calculated for each total concentration of the β-CD following Mendoza et al. method.[25]

$$D_{app} = (D_f - D_c)\chi_f + D_c \quad (3)$$

To obtain the D_c for each glycoconjugate/β-CD complex, we constructed linear plots of D_{app} data versus χ_f. The plots would provide D_c values from the intercept on the ordinate axis. The best fit to the data yielded the straight lines shown in Figure 8. It can be observed, however, that at χ_f values lower than 0.3, that is, at concentrations of β-CD higher than 1 mM, data points deviate from the line, suggesting that

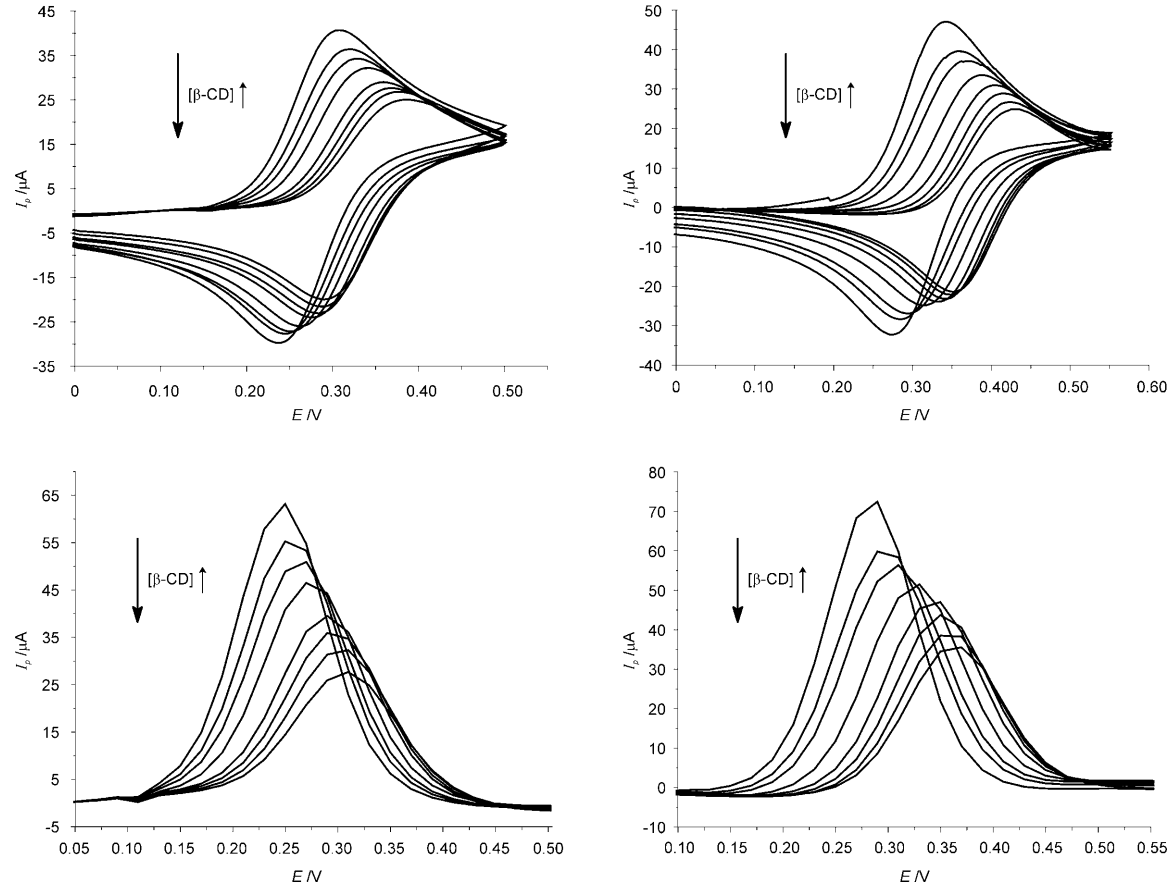


Figure 6. Cyclic (top, sweep rate = 0.1 $V s^{-1}$) and differential pulse (bottom, sweep rate = 0.01 $V s^{-1}$) voltammetry curves of ferrocene–carbohydrate conjugates **15** (left) and **34** (right) in 0.5 mM aqueous solution with 50 mM NaCl as supporting electrolyte in the presence of increasing concentrations of β-CD ranging from 0 to 5 mM at 21 °C.

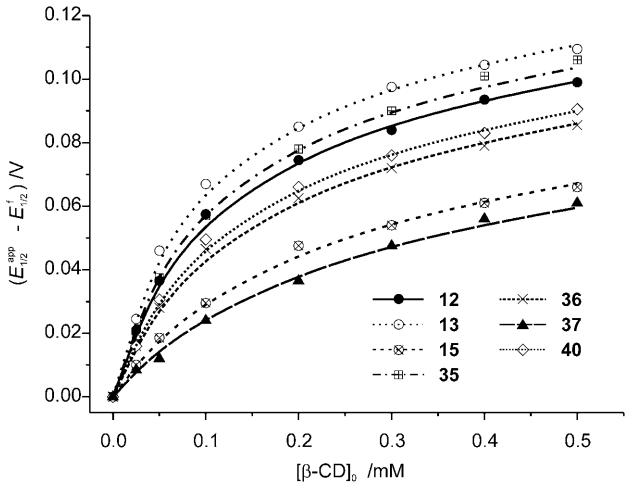


Figure 7. Graphical plot of $(E^{app}_{1/2} - E^{f}_{1/2})$ data from CV experiments (sweep rate = 0.1 $V s^{-1}$) versus total concentration of β-CD for glycoconjugates **12**, **13**, **15**, **35**, **36**, **37** and **40** in 0.5 mM aqueous solutions with 50 mM NaCl as supporting electrolyte at 21 °C and nonlinear least-square fittings to the model proposed by Mendoza et al.[25]

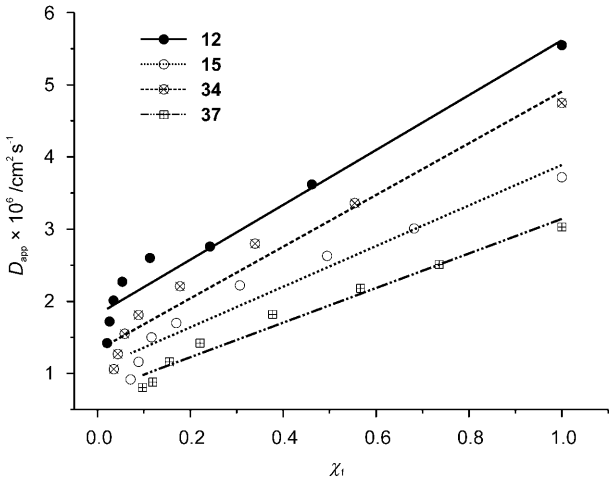


Figure 8. Graphical plot of apparent diffusion coefficient (D_{app}) versus mole fraction of free guest for glycoconjugates **12**, **15**, **34** and **37** in 0.5 mM aqueous solutions with 50 mM NaCl at 21 °C and linear least-square fittings to the Equation (3).

perhaps at higher host concentrations, the decrease of the D_{app} values is even more marked. According to the Stokes–Einstein equation, the diffusion coefficient value is inversely proportional to the viscosity of the solution. Hence, the marked decrease of the D_{app} values could be related with an increase of the viscosity due to the macrocycle. In fact, it

has been shown recently the dependence of the diffusion coefficient of β-CD on its concentration in aqueous solution,[28] this behaviour being expressed by the proposed Equation (4), in which D_0^* is the observed diffusion coefficient, D_0^0 is the diffusion coefficient at infinite dilution, A is a proportionality constant and $[\beta\text{-CD}]_0$ is the total concentration of the cyclodextrin.

$$D_0^* = D_0^0(1 + A[\beta\text{-CD}]_0) \quad (4)$$

To incorporate this effect on the calculation of the D_c values, Equations (3) and (4) were combined to give Equation (5), in which $[G]_0$ is the total concentration of the electroactive guest.

$$D_{app} = [(D_f - D_c)\chi_f + D_c]\left[1 + A(1-\chi_f)\left(\frac{1 + K[G]_o\chi_f}{K\chi_f}\right)\right] \quad (5)$$

The best fit of the data to the Equation (5) (using K values obtained from calorimetry) is displayed in Figure 9 and showed very high correlation coefficients with r^2 values

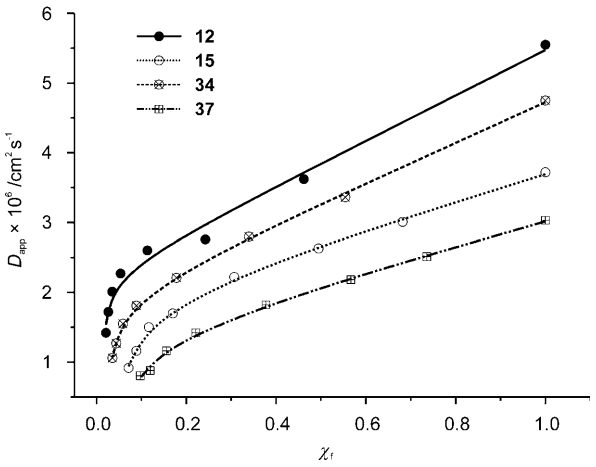


Figure 9. Graphical plot of apparent diffusion coefficient (D_{app}) versus mole fraction of free guest for glycoconjugates **12**, **15**, **34** and **37** in 0.5 mM aqueous solutions with 50 mM NaCl at 21 °C and nonlinear least-square fittings to Equation (5).

between 0.990 and 0.998, which would support our previous assumption. In addition, we found a good correlation between the D_f values estimated from the Randles–Ševčik equation [Eq. (2)] and those obtained from Equation (5) (Table 1), with the exception of **16**, the D_f values of which show the highest deviation. The D_c values obtained for the complexes formed by β-CD and the monosubstituted ferrocene glycoconjugates **12**–**14**, **34**–**36**, **40** and **41** vary from 1.29×10^{-6} and 3.70×10^{-6} cm^{2}s^{-1}. In the case of bis-substituted ferrocene glycoconjugates **15**, **16**, **37** and **38**, with larger supramolecular size, D_c values range from 1.1×10^{-6} to 2.24×10^{-6} cm^{2}s^{-1}. When the D_f and D_c values are compared, a diminishing of the latter is observed, as one would expect from the increase of the hydrodynamic radius of the complex, the D_c/D_f ratios being within the interval 0.33 and 0.63.[29]

Conclusion

A series of electroactive glycoconjugates based on a ferrocene core bearing substituents on one or both of its cyclopentadienyl rings has been synthesised by two convenient methods. The first method involves the reaction in acidic media of 1-thioglycosides with ferrocenemethanol or 1,1′-ferrocenedimethanol. In the second method, we used the regiospecific Cu^I-catalysed cycloaddition of propargyl glycosides or azido-functionalised *O*-glycosides with azido ferrocene derivatives or 1-ethynylferrocene, respectively. The analysis of the NMR, calorimetric and electrochemical data (ROESY, redox potentials, diffusion coefficients for both free guests and the complexes, and the ΔH, ΔS and K values) showed that:

1) The obtained carbohydrate–ferrocene conjugates exhibit reversible oxidation and reduction of the ferrocene core.
2) Their redox potentials are dependent on the chemical nature of the tether and the number of substituents.
3) All ferrocene derivatives, whether bearing the saccharide attached to one or to both cyclopentadienyl rings, form stable complexes with β-cyclodextrin through the inclusion of the ferrocene core into the cyclodextrin cavity.
4) The ferrocene moiety adopts within the cavity an equatorial orientation when both ferrocene rings are substituted, while when bearing one saccharide it adopts an axial or equatorial orientation depending on the nature of the substituent.
5) Although the enthalpy of complexation with the β-cyclodextrin is mainly provided by the ferrocene moiety, the carbohydrate moiety can modulate the thermodynamics of binding.

Finally, it has been shown that ferrocene-bearing glycoconjugates can be used as redox probes for the electrochemical monitoring of binding interactions with receptors when the ferrocene moiety is involved. We are presently working on the study of the binding interactions of these glycoconjugates with lectins. The results of these investigations will be published in due course.

Experimental Section

General methods: TLC was performed on Merck Silica Gel 60 F_{254} aluminium sheets and developed by UV light and ethanolic sulfuric acid (5% v/v). Flash column chromatography was performed on Merck Silica Gel (230–400 mesh, ASTM). Melting points were measured on a Gallenkamp and a Büchi B-450 melting point apparatus and are uncorrected. Optical rotations were recorded on a Perkin–Elmer 141 and an ADP 220 polarimeter at room temperature. IR spectra were recorded on a Mattson Satellite FTIR and a Mattson Genesis II FTIR. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX 300 MHz spectrometer. Chemi-

cal shifts are given in ppm and referenced to internal TMS. DEPT135, COSY, HMQC, HMBC and selective 1D-TOCSY experiments were used when necessary. 2D-ROESY experiments were recorded on a Bruker Avance DPX Ultrashield 500 MHz spectrometer. FAB mass spectra were recorded on a Micromass VG Autospec-Q spectrometer. MALDI-TOF mass spectra were recorded on a Bruker Autoflex spectrometer. Solvents were dried according to literature procedures.[30] Pure water (MilliQ, 18.2 MΩ cm) was obtained from a Millipore MilliQ Plus system. Ferrocenemethanol (**1**), 1,1′-bis(hydroxymethyl)ferrocene (**8**) and 1-ethynylferrocene (**29**) were purchased from Aldrich and used as received. β-CD was purchased from CycloLab and dried at 50 °C in vacuum in the presence of P_2O_5 until constant weigh. Glycosyl thiols[31] (**2–4**), propargyl glycosides[32] (**20–22**) and 2-azidoethyl glycosides[33] (**30–31**) were prepared as reported.

Cyclic voltammetry (CV) and differential pulse voltammetry (DPV) experiments were carried out in nitrogen-purged (180 s) MilliQ water solutions with a Metrohm 663 VA-Stand instrument interfaced to an Autolab PSTAT10 potentiostat connected to a computer running Eco Chimie B. V. GPES 4.9 software. Temperature of the solutions was measured with a digital thermometer Digi-sense J Thermocouple. The working electrodes were an Ingold Swiss Made Pt805NS-M5 platinum ring electrode (∅ 5 mm, effective area 0.399 ± 0.009 cm^2) and a Radiometer Type 101 platinum sheet electrode (6×4 mm, effective area 0.410 ± 0.003 cm^2). They were immersed into a H_2SO_4 50 % v/v solution for 5 min and sonicated in MilliQ water for 10 min before each experiment. The counter electrode was a Metrohm 6.1247.000 glassy carbon electrode (65 mm, Ø 2 mm), which was immersed into a 0.1 M HNO_3 solution for 5 min, carefully polished with a basic Al_2O_3–water slurry and sonicated in a H_2O/MeOH/CH_3CN 1:1:1 mixture at 40 °C for 10 min prior to use. A Metrohm 6.0724.140 Ag/AgCl (3 M KCl) electrode was used as reference. Electrochemical behaviour of each conjugate was studied on 0.5 mM solutions with 50 mM NaCl as supporting electrolyte. Cyclic voltammograms were obtained measuring five scans at six sweep rates varying from 0.05–0.5 V s^{-1} with a step potential of 0.002 V. DPV experiments were measured three times with a scan rate of 0.01 V s^{-1}, a step potential of 0.02 V, a modulation amplitude of 0.05 V, a modulation time of 0.05 s and an interval time of 2 s. A solution of 50 mM NaCl was used as blank and its signal was subtracted from those of the compounds. The diffusion coefficients were calculated by fitting the anodic peak current versus square root of the sweep rate plots to the Randles-Ševčik equation [Eq. (2)]. The effective area of the working electrodes were determined with the same method by using $Na_4Fe(CN)_6$ (1 mM in MilliQ water, 100 mM KCl as supporting electrolyte, $D_0 = 0.65 \times 10^{-5}$ cm^2 s^{-1}) as the electroactive species.[34] These voltammetric experiments were repeated for each conjugate at a scan rate of 0.1 V s^{-1} in the presence of increasing amounts of β-CD varying from 0 to 5 mM. A solution of 5 mM β-CD in 50 mM NaCl was used as blank at this time. The stability constants (K and K_{ox}) of the complexes were obtained through the ($E_{app}^{1/2} - E_f^{1/2}$) versus [β-CD]$_0$ plots by the method described by Mendoza et al.[25] Fittings were made by using OriginPro v7.5 software.

Isothermal titration calorimetry experiments were performed using an MCS isothermal titration calorimeter (ITC) from Microcal, Inc. (Northampton, MA).[35] The calorimeter was calibrated by known heat pulses as recommended by the manufacturer. During titration, the reference cell was filled with MilliQ water. Solutions of the conjugates (0.5–0.9 mM) and β-CD (12.13 mM) were prepared in 20 mM phosphate buffer (pH 7.0) with 20 mM NaCl and degassed for 10 min under vacuum prior to the titration experiments. The sample cell was filled with each conjugate, and 250 μL of β-CD were injected in 10 μL portions every 300 s. During the titration, the reaction mixture was continuously stirred at 400 rpm. The background titration profiles, under identical experimental conditions, were obtained by injecting the β-CD into pure buffer. The dilution heats were concentration independent and identical to the heat signals detected after the saturation was reached. The raw experimental data were presented as the amount of heat produced per second following each injection of CD into the conjugate solution (corrected for the macrocycle heats of dilution) as a function of time. The amount of heat produced per injection was calculated by integration of the area under individual peaks by the Origin software provided with the instrument. The errors are provided by software from the best fit of the experimental data to the model of equal and independent sites, and correspond to the standard deviation in the fitting of the curves.

General procedure for the synthesis of thioglycosylated ferrocenes 5–7 and 9–11: Trifluoroacetic acid (3 equiv per ferrocene hydroxyl group) was added to a solution of ferrocene derivative **1** or **8** and glycosyl thiol **2–4** (1.1 equiv per ferrocene hydroxyl group) in dry CH_2Cl_2 (10 mL). The mixture was stirred for 2 h at room temperature. The solvent was removed by evaporation under vacuum and the crude was purified by column chromatography to yield the corresponding thioglycosylated ferrocene.

(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyl)thiomethylferrocene (5): Starting from **1** (25 mg, 0.116 mmol), column chromatography (EtOAc/hexane 1:2) gave **5** (61 mg, 94 %) as a yellow solid. M.p. 140–141 °C; $[\alpha]_D^{25} = -30$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.19$ (t, $^3J =$ 9.2 Hz, 1H; H-3), 5.07 (t, $^3J = 10.7$ Hz, 1H; H-4), 5.04 (t, $^3J = 10.0$ Hz, 1H; H-2), 4.40 (d, ^3J(H1,H2) = 9.8 Hz, 1H; H-1), 4.26 (dd, ^2J(H6,H6′) = 12.3 Hz, ^3J(H5,H6) = 5.0 Hz, 1H; H-6), 4.14 (s, 5H; H$_{Cp'}$), 4.20 (brs, 2H; H$_{Cp}$), 4.12 (brs, 3H; H$_{Cp}$, H-6′), 3.74 (d, $^2J = 13.1$ Hz, 1H; CHS), 3.67 (m, 1H; H-5), 3.65 (d, $^2J = 12.9$ Hz, 1H; CHS), 2.11 (s, 3H; CH_3CO), 2.02 (s, 6H; CH_3CO), 3.99 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 169.4$ (CO), 83.5 (C$_{ipso}$), 82.5 (C-1), 75.8 (C-5), 73.9 (C-3), 69.8 (C-2), 68.9 (C$_{Cp}$), 68.8 (C$_{Cp'}$), 68.6, 68.4 (C$_{Cp}$), 68.3 (C-4), 68.0 (C$_{Cp}$), 62.2 (C-6), 29.5 (CH_2S), 20.8, 20.7, 20.6 ppm (CH_3CO); IR (KBr): $\tilde{\nu} = 2951$, 2901, 2858, 1735, 1376, 1229, 1043 cm^{-1}; HRMS (FAB): m/z calcd for $C_{25}H_{30}O_9SFe$: 562.0960; found: 585.0858 $[M+Na]^+$.

(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyl)thiomethylferrocene (6): Starting from **1** (50 mg, 0.231 mmol), column chromatography (EtOAc/hexane 1:2) gave **6** (117 mg, 90 %) as a yellow solid. M.p. 150–151 °C; $[\alpha]_D^{25} = +78$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.30$ (brs, 1H; H-2), 5.29 (brd, $^3J = 1.0$ Hz, 1H, H-4), 5.26 (t, $^3J = 3.1$ Hz, 1H; H-3), 5.20 (brs, 1H; H-1), 4.38–4.34 (m, 1H; H-5), 4.32 (dd, ^2J(H6,H6′) = 12.4 Hz, ^3J(H5,H6) = 5.9 Hz, 1H; H-6), 4.20 (d, $^3J = 1.7$ Hz, 1H; H$_{Cp}$), 4.18 (d, $^3J = 1.7$ Hz, 1H; H$_{Cp}$), 4.14–4.11 (m, 2H; H$_{Cp}$), 4.13 (s, 5H; H$_{Cp'}$), 4.07 (brd, ^2J(H6,H6′) = 12.4 Hz, 1H; H-6′), 3.65 (d, $^2J = 13.5$ Hz, 1H; CHS), 3.57 (d, $^2J = 13.6$ Hz, 1H; CHS), 2.14 (s, 3H; CH_3CO), 2.13 (s, 3H; CH_3CO), 2.04 (s, 3H; CH_3CO), 1.97 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.4$, 169.7, 169.6, 169.5 (CO), 83.4 (C$_{ipso}$), 81.7 (C-1), 70.6 (C-2), 69.5 (C-3), 68.8 (C-5), 68.7 (C$_{Cp}$), 68.6 (C$_{Cp'}$), 68.5, 68.3, 68.0 (C$_{Cp}$), 66.2 (C-4), 62.3 (C-6), 30.7 (CH_2S), 20.8, 20.6, 20.5, 20.4 ppm (CH_3CO); IR (KBr): $\tilde{\nu} = 2968$, 2950, 1746, 1370, 1226, 1054 cm^{-1}; HRMS (FAB): m/z calcd for $C_{25}H_{30}O_9SFe$: 562.0960; found: 585.0855 $[M+Na]^+$.

[2,3,6-Tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]thiomethylferrocene (7): Starting from **1** (50 mg, 0.231 mmol), column chromatography (diethyl ether/hexane 4:1) gave **7** (184 mg, 93 %) as a yellow solid. M.p. 87–90 °C; $[\alpha]_D^{25} = -17$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.33$ (brd, $^3J = 2.8$ Hz, 1H; H-4′), 5.14 (t, $^3J = 9.1$ Hz, 1H; H-3), 5.08 (dd, ^3J(H2′,H3′) = 10.4 Hz, ^3J(H1′,H2′) = 7.8 Hz, 1H; H-2′), 4.93 (dd, ^3J(H1,H2) = 10.6 Hz, ^3J(H2,H3) = 3.0 Hz, 1H; H-2), 4.92 (t, $^3J = 9.8$ Hz, 1H; H-3′), 4.46 (d, ^3J(H1′,H2′) = 8.0 Hz, 1H; H-1′), 4.46 (brd, ^2J(H6,H6) = 13.5 Hz, 1H; H-6), 4.36 (d, 1H, ^3J(H1,H2) = 10.5 Hz, 1H; H-1), 4.18 (brs, 1H; H$_{Cp}$), 4.12 (s, 5H; H$_{Cp'}$), 4.10–4.02 (m, 6H; H$_{Cp}$, H-6,6′,6′), 3.85 (t, $^3J = 7.0$ Hz, 1H; H-5′), 3.78 (t, $^3J = 9.5$ Hz, 1H; H-4), 3.69 (d, $^2J = 13.0$ Hz, 1H; CHS), 3.60 (d, $^2J =$ 13.2 Hz, 1H; CHS), 3.54 (ddd, ^3J(H4,H5) = 9.8 Hz, ^3J(H5,H6) = 5.5 Hz, ^3J(H5,H6) = 1.7 Hz, 1H; H-5), 2.14 (s, 3H; CH_3CO), 2.13 (s, 3H; CH_3CO), 2.04 (s, 6H; CH_3CO), 2.02 (s, 3H; CH_3CO), 1.99 (s, 3H; CH_3CO), 1.95 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.3$, 170.1, 170.0, 169.6, 169.5 169.0 (CO), 101.0 (C-1′), 83.4 (C$_{ipso}$), 82.1 (C-1), 76.5 (C-5), 76.2 (C-4), 73.7 (C-3), 70.9 (C-3′), 70.6 (C-5′), 70.2 (C-2), 69.0 (C-2′), 68.8 (C$_{Cp}$), 68.7 (C$_{Cp'}$), 68.5, 68.4, 67.9 (C$_{Cp}$), 66.5 (C-4′), 62.3 (C-6), 60.7 (C-6′), 29.6 (CH_2S), 20.8, 20.7, 20.6, 20.5, 20.4 ppm (CH_3CO); IR (KBr): $\tilde{\nu} = 2953$, 2924, 2853, 1751, 1370, 1230, 1047 cm^{-1}; HRMS (FAB): m/z calcd for $C_{37}H_{46}O_{17}SFe$: 850.1805; found: 873.1701 $[M+Na]^+$.

1,1′-Bis[(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)thiomethyl]ferrocene (9): Starting from **8** (50 mg, 0.203 mmol), column chromatography (EtOAc/hexane 1:2→3:2) gave **9** (175 mg, 92 %) as a yellow solid. M.p. 80–81 °C; $[\alpha]_D^{25} = -37$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$):

$\delta = 5.19$ (t, $^3J = 9.2$ Hz, 2H; H-3), 5.09 (t, $^3J = 9.5$ Hz, 2H; H-4), 5.04 (t, $^3J = 9.5$ Hz, 2H; H-2), 4.41 (d, ^3J(H1,H2) = 9.9 Hz, 2H; H-1), 4.26 (dd, ^2J(H6,H6′) = 12.4 Hz, ^3J(H5,H6) = 4.8 Hz, 2H; H-6), 4.17 (m, 2H; H-6′), 4.13 (brs, 8H; H_{Cp}), 3.71 (d, $^2J = 13.0$ Hz, 2H; CHS), 3.69–3.63 (m, 2H; H-5), 3.65 (d, $^2J = 13.1$ Hz, 2H; CH_2S), 2.12 (s, 6H; CH_3CO), 2.03 (s, 6H; CH_3CO), 2.02 (s, 6H; CH_3CO), 2.00 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.6$, 170.1, 169.4 (CO), 84.0 (C_{ipso}), 82.5 (C-1), 75.8 (C-5), 73.8 (C-3), 69.7 (C-2), 69.6, 69.4, 69.3, 68.9 (C_{Cp}), 68.4 (C-4), 62.3 (C-6), 29.2 (CH_2S), 20.8, 20.7, 20.6 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2945, 2868, 1751, 1370, 1225, 1037 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{40}H_{50}O_{18}S_2Fe$: 938.1788; found: 961.1686 $[M+Na]^+$.

1,1′-Bis[(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyl)thiomethyl]ferrocene (10): Starting from **8** (50 mg, 0.203 mmol), column chromatography (EtOAc/hexane 1:2→3:2) gave **10** (167 mg, 87%) as a yellow solid. M.p. 146–148 °C; $[\alpha]_D^{25} = +79$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.34$–5.29 (m, 2H; H-4), 5.28 (brs, 2H; H-2), 5.23 (dd, ^3J(H3,H4) = 10.0 Hz, ^3J(H2,H3) = 2.3 Hz, 2H; H-3), 5.19 (brs, 2H; H-1), 4.36–4.31 (m, 2H; H-5), 4.31 (dd, ^2J(H6,H6′) = 10.9 Hz, ^3J(H5,H6) = 4.8 Hz, 2H; H-6), 4.18 (brs, 2H; H_{Cp}), 4.16 (d, $^3J = 1.5$ Hz, 2H; H_{Cp}), 4.12 (t, $^3J = 1.7$ Hz, 4H; H_{Cp}), 4.07 (d, $^2J = 10.1$ Hz, 2H; H-6′), 3.62 (d, ^2J = 13.6 Hz, 2H; CHS), 3.55 (d, $^2J = 13.6$ Hz, 2H; CHS), 2.14 (s, 6H; CH_3CO), 2.13 (s, 6H; CH_3CO), 2.04 (s, 6H; CH_3CO), 1.97 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.5$, 169.8, 169.7, 169.6 (CO), 84.0 (C_{ipso}), 81.9 (C-1), 70.7 (C-2), 69.6 (C-3), 69.5 (C-5, C_{Cp}), 69.4, 69.1, 69.0 (C_{Cp}), 66.3 (C-4), 62.4 (C-6), 30.6 (CH_2S), 20.9, 20.8, 20.7, 20.6 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2950, 2925, 1749, 1369, 1226, 1049 cm^{-1}; MS (MALDI-TOF): *m*/*z* calcd for $C_{40}H_{50}O_{18}S_2Fe$: 938.179; found: 938.174 $[M]^+$, 939.168 $[M+H]^+$, 961.182 $[M+Na]^+$.

1,1′-Bis{[2,3,6-tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyl]thiomethyl}ferrocene (11): Starting from **8** (30 mg, 0.122 mmol), column chromatography (EtOAc/hexane 2:1) gave **11** (168 mg, 91%) as a yellow solid. M.p. 110–114 °C; $[\alpha]_D^{25} = -21$ ($c = 1$ in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 5.25$ (brs, 2H; H-4′), 5.08 (t, $^3J = 9.2$ Hz, 2H; H-3), 5.01 (dd, ^3J(H2′,H3′) = 10.3 Hz, ^3J(H1′,H2′) = 7.9 Hz, 2H; H-2′), 4.88 (dd, ^3J(H1,H2) = 10.3 Hz, ^3J(H2,H3) = 3.4 Hz, 2H; H-2), 4.84 (t, $^3J = 9.7$ Hz, 2H; H-3′), 4.42 (d, ^3J(H1′,H2′) = 7.6 Hz, 2H; H-1′), 4.39 (brd, ^2J(H6,H6) = 9.5 Hz, 2H; H-6), 4.31 (d, ^3J(H1,H2) = 10.0 Hz, 2H; H-1), 4.08 (brs, 2H; H_{Cp}), 4.03 (brs, 12H; H_{Cp}, H-6,6′,6′), 3.81 (t, $^3J = 6.7$ Hz, 2H; H-5′), 3.71 (t, $^3J = 9.5$ Hz, 2H; H-4), 3.60 (d, ^2J = 13.1 Hz, 2H; CHS), 3.52 (d, $^2J = 12.9$ Hz, 2H; CHS), 3.52–3.47 (m, 2H; H-5), 2.07 (s, 6H; CH_3CO), 2.06 (s, 6H; CH_3CO), 1.97 (s, 12H; CH_3CO), 1.95 (s, 6H; CH_3CO), 1.93 (s, 6H; CH_3CO), 1.88 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 170.1$, 169.9, 169.8, 169.4, 169.3, 168.8 (CO), 100.8 (C-1′), 83.8 (C_{ipso}), 82.0 (C-1), 76.4 (C-5), 76.0 (C-4), 73.5 (C-3), 70.7 (C-3′), 70.4 (C-5′), 69.9 (C-2), 69.3 (C-2′), 69.1, 68.9, 68.6 (C_{Cp}), 66.4 (C-4′), 62.1 (C-6), 60.6 (C-6′), 29.1 (CH_2S), 20.7, 20.5, 20.4, 20.3, 20.2 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2938, 2871, 1735, 1370, 1232, 1046 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{64}H_{82}O_{34}S_2Fe$: 1514.3478; found: 1537.3379 $[M+Na]^+$.

General procedure for the Zemplén de-*O*-acetylation of thioglycosylated ferrocenes 5–7 and 9–11: A solution of thioglycosylated ferrocene **5**–**7** or **9**–**11** in dry MeOH (15–20 mL) or in a mixture of dry MeOH and dry CH_2Cl_2 10:1 (15–20 mL) was made alkaline to pH 9–10 (indicator paper) with a fresh solution of NaOMe in methanol (1 M) and stirred at room temperature for 2–24 h following the reaction by TLC. If the product precipitated, the solvent was concentrated under vacuum to 1–2 mL and diethyl ether was added. The solid was filtered off and washed with diethyl ether. In other cases, the solvent was removed under vacuum and the crude was purified by column chromatography. The pure compound was dissolved in water and lyophilised.

β-D-Glucopyranosylthiomethylferrocene (12): Starting from **5** (173 mg, 0.308 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 3:2) gave **12** (118 mg, 98%) as a yellow solid. M.p. 144–146 °C; $[\alpha]_D^{25} = -40$ ($c = 0.25$ in MeOH); ^{1}H NMR (300 MHz, D_2O, 60 °C): $\delta = 4.79$ (d, ^3J(H1,H2) = 9.7 Hz, 1H; H-1), 4.71 (brs, 2H; H_{Cp}), 4.68 (brs, 2H; H_{Cp}), 4.63 (s, 5H; $H_{Cp'}$), 4.24 (d, ^2J(H6,H6′) = 12.5 Hz, 1H; H-6), 4.21 (d, ^2J = 13.3 Hz, 1H; CHS), 4.15 (d, $^2J = 13.3$ Hz, 1H; CHS), 4.06 (dd, ^2J(H6,H6′) = 12.5 Hz, ^3J(H5,H6′) = 4.9 Hz, 1H; H-6′), 3.84–3.75 (m, 3H; H-3,4,5), 3.67 ppm (t, $^3J = 9.4$ Hz, 1H; H-2); ^{13}C NMR (75 MHz, D_2O, 60 °C): $\delta = 85.0$ (C-1), 84.9 (C_{ipso}), 80.2 (C-5), 77.8 (C-3), 72.7 (C-2), 70.1 (C-4), 69.5 (C_{Cp}), 69.3 ($C_{Cp'}$), 69.1, 68.8, 68.5 (C_{Cp}), 61.4 (C-6), 29.9 ppm (CH_2S); IR (KBr): $\tilde{\nu}$ = 3369, 2922, 2856, 1019 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{22}O_5SFe$: 394.0538; found: 417.0433 $[M+Na]^+$.

α-D-Mannopyranosylthiomethylferrocene (13): Starting from **6** (104 mg, 0.185 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 3:2) gave **13** (69 mg, 95%) as a yellow solid. M.p. 168 °C; $[\alpha]_D^{25} = +154$ (c = 0.25 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 5.18$ (d, ^3J(H1,H2) = 1.3 Hz, 1H; H-1), 4.25 (dd, $^3J = 3.5$ Hz, $^3J = 1.5$ Hz, 1H; H_{Cp}), 4.22 (dd, $^3J = 3.5$ Hz, $^3J = 1.6$ Hz, 1H; H_{Cp}), 4.15 (s, 5H; $H_{Cp'}$), 4.12 (t, $^3J = 1.6$ Hz, 2H; H_{Cp}), 3.94–3.90 (m, 1H; H-5), 3.86 (dd, ^2J(H6,H6′) = 11.8 Hz, ^3J(H5,H6) = 2.3 Hz, 1H; H-6), 3.82 (dd, ^3J(H2,H3) = 3.0 Hz, ^3J(H1,H2) = 1.5 Hz, 1H; H-2), 3.75 (dd, ^2J(H6,H6′) = 11.8 Hz, ^3J(H5,H6′) = 5.9 Hz, 1H; H-6′), 3.69 (d, $^2J = 13.6$ Hz, 1H; CHS), 3.68–3.62 (m, 2H; H-3,4), 3.59 ppm (d, $^2J = 13.6$ Hz, 1H; CHS); ^{13}C NMR (75 MHz, CD_3OD): δ = 85.9 (C_{ipso}), 85.4 (C-1), 74.9 (C-5), 73.5 (C-2), 73.3 (C-3), 70.2 (C_{Cp}), 69.7 ($C_{Cp'}$), 69.6 (C_{Cp}), 69.4 (C-4), 68.9, 68.8 (C_{Cp}), 62.8 (C-6), 31.0 ppm (CH_2S); IR (KBr): $\tilde{\nu}$ = 3396, 2922, 2858, 1069 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{17}H_{22}O_5SFe$: 394.0538; found: 417.0433 $[M+Na]^+$

4-*O*-(β-D-Galactopyranosyl)-β-D-glucopyranosylthiomethylferrocene (14): Starting from **7** (158 mg, 0.186 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 2:1) gave **14** (78 mg, 76%) as a yellow solid. M.p. 166 °C (decomp); $[\alpha]_D^{25} = -28$ (c = 0.25 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 4.36$ (d, ^3J(H1′,H2′) = 7.3 Hz, 1H; H-1′), 4.34 (d, ^3J(H1,H2) = 9.7 Hz, 1H; H-1), 4.25 (dd, $^3J = 3.4$ Hz, $^3J = 1.5$ Hz, 1H; H_{Cp}), 4.22 (dd, $^3J = 3.4$ Hz, $^3J = 1.5$ Hz, 1H; H_{Cp}), 4.15 (s, 5H; $H_{Cp'}$), 4.12 (t, ^3J = 1.8 Hz, 2H; H_{Cp}), 3.94 (dd, ^3J(H6,H6) = 12.2 Hz, ^3J(H5,H6) = 2.4 Hz, 1H; H-6), 3.83 (dd, ^2J(H6,H6) = 12.0 Hz, ^3J(H5,H6) = 4.3 Hz, 1H; H-6), 3.82 (d, $^2J = 13.2$ Hz, 1H; CHS), 3.81 (brs, 1H; H-4′), 3.78 (dd, ^2J(H6′,H6′) = 11.3 Hz, ^3J(H5′,H6′) = 7.4 Hz, 1H; H-6′), 3.70 (dd, ^2J(H6′,H6′) = 11.3 Hz, ^3J(H5′,H6′) = 4.4 Hz, 1H; H-6′), 3.69 (d, $^2J = 13.2$ Hz, 1H; CHS), 3.60–3.57 (m, 1H; H-5′), 3.58 (t, $^3J = 9.2$ Hz, 1H; H-4), 3.55 (dd, ^3J(H2′,H3′) = 9.6 Hz, ^3J(H1′,H2′) = 7.4 Hz, 1H; H-2′), 3.48 (dd, ^3J(H2′,H3′) = 9.7 Hz, ^3J(H3′,H4′) = 3.3 Hz, 1H; H-3′), 3.46 (t, $^3J = 8.7$ Hz, 1H; H-3), 3.37 (ddd, ^3J(H4,H5) = 9.6 Hz, ^3J(H5,H6) = 4.3 Hz, ^3J(H5,H6) = 2.5 Hz, 1H; H-5), 3.28 ppm (dd, ^3J(H1,H2) = 9.7 Hz, ^3J(H2,H3) = 8.8 Hz, 1H; H-2); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 105.0$ (C-1′), 85.8 (C-1), 85.7 (C_{ipso}), 80.5 (C-4), 80.4 (C-5), 78.0 (C-3), 77.1 (C-5′), 74.8 (C-3′), 74.1 (C-2), 72.5 (C-2′), 70.3 (C-4′), 70.2, 69.8 (C_{Cp}), 69.7 ($C_{Cp'}$), 69.1, 68.8 (C_{Cp}), 62.5 (C-6′), 62.1 (C-6), 30.4 ppm (CH_2S); IR (KBr): $\tilde{\nu}$ = 3402, 2918, 2859, 1077 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{23}H_{32}O_{10}SFe$: 556.1066; found: 579.0963 $[M+Na]^+$.

1,1′-Bis(β-D-glucopyranosylthiomethyl)ferrocene (15): Starting from **9** (176 mg, 0.187 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 2:1) gave **15** (108 mg, 96%) as a yellow solid. M.p. 65 °C (decomp); $[\alpha]_D^{25} = -32$ (c = 0.25 in MeOH); ^{1}H NMR (300 MHz, D_2O, 60 °C): $\delta = 4.78$ (d, ^3J(H1,H2) = 9.7 Hz, 2H; H-1), 4.70 (m; H_{Cp}, HDO), 4.64 (d, $^3J = 7.7$ Hz, 4H; H_{Cp}), 4.24 (d, ^2J(H6,H6′) = 12.5 Hz, 2H; H-6), 4.20 (brdd, $^2J = 11.8$ Hz, 4H; CH_2S), 4.06 (dd, ^2J(H6,H6′) = 12.9 Hz, ^3J(H5,H6′) = 4.5 Hz, 2H; H-6′), 3.84–3.75 (m, 6H; H-3,4,5), 3.67 ppm (t, $^3J = 9.3$ Hz, 2H; H-2); ^{13}C NMR (75 MHz, D_2O, 60 °C): $\delta = 85.4$ (C_{ipso}), 85.0 (C-1), 80.2 (C-5), 77.8 (C-3), 72.7 (C-2), 70.3, 70.1, 69.9, 69.7, 69.5 (C_{Cp}, C-4), 61.5 (C-6), 29.7 ppm (CH_2S); IR (KBr): $\tilde{\nu}$ = 3396, 2920, 2880, 1032 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{24}H_{34}O_{10}S_2Fe$: 602.0943; found: 625.0830 $[M+Na]^+$.

1,1′-Bis(α-D-mannopyranosylthiomethyl)ferrocene (16): Starting from **10** (162 mg, 0.173 mmol) in dry MeOH–CH_2Cl_2 10:1, column chromatography (EtOAc/MeOH 2:1) gave **16** (99 mg, 95%) as a yellow solid. M.p. 73–74 °C; $[\alpha]_D^{25} = +190$ (c = 0.25 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta = 5.18$ (s, 2H; H-1), 4.22 (s, 2H; H_{Cp}), 4.19 (s, 2H; H_{Cp}), 4.13 (brs, 4H; H_{Cp}), 3.94–3.90 (m, 2H; H-5), 3.86 (dd, ^2J(H6,H6′) = 12.1 Hz, ^3J(H5,H6) = 2.3 Hz, 2H; H-6), 3.83 (brs, 2H; H-2), 3.75 (dd, ^2J(H6,H6′) = 11.7 Hz, ^3J(H5,H6′) = 5.8 Hz, 2H; H-6′), 3.68 (d, $^2J = 13.6$ Hz, 2H; CHS), 3.64 (brs, 4H; H-3,4), 3.59 ppm (d, $^2J = 13.6$ Hz, 2H; CH_2S); ^{13}C NMR (75 MHz, CD_3OD): $\delta = 86.3$ (C_{ipso}), 85.4 (C-1), 74.9 (C-5), 73.4 (C-2), 73.3 (C-3), 71.0, 70.5, 70.0, 69.7 (C_{Cp}), 68.9 (C-4), 62.8 (C-6), 30.8 ppm

(CH_2S); IR (KBr): $\tilde{\nu}$ = 3426, 2919, 2876, 1067 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{24}H_{34}O_{10}S_2Fe$: 602.0943; found: 625.0861 $[M+Na]^+$.

1,1′-Bis[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosylthiomethyl]ferrocene (17): Starting from **11** (168 mg, 0.111 mmol) in dry MeOH, precipitation with diethyl ether gave **17** (86 mg, 83%) as a yellow solid. M.p. 179°C (decomp); $[\alpha]_D^{25} = -56$ (*c* = 0.125 in MeOH); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 5.24 (d, ^3J = 5.7 Hz, 2H; OH), 5.10 (brs, 2H; OH), 4.80 (brs, 2H; OH), 4.73 (s, 2H; OH), 4.69–4.64 (m, 4H; OH), 4.52 (d, ^3J = 4.2 Hz, 2H; OH), 4.19 (d, ^3J(H1′,H2′) = 8.8 Hz, 2H; H-1′), 4.18 (d, ^3J(H1,H2) = 9.5 Hz, 2H; H-1), 4.17 (t, ^3J = 1.8 Hz, 4H; H_{Cp}), 4.10 (dd, ^3J = 3.6 Hz, ^3J = 1.8 Hz, 4H; H_{Cp}), 3.82 (dd, ^2J(H6,H6) = 11.0 Hz, ^3J-(H5,H6) = 4.7 Hz, 2H; H-6), 3.75 (d, ^2J = 13.3 Hz, 2H; CHS), 3.61–3.58 (brm, 4H; H-3′,6), 3.57 (d, ^2J = 13.3 Hz, 2H; CHS), 3.53–3.43 (m, 6H; H-5′,6′,6′), 3.31 (brs, 4H; H-2′,4′), 3.26 (brd, 6H; H-3,4,5), 3.11–3.03 ppm (brm, 2H; H-2); ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 103.8 (C-1′), 84.9 (C_{ipso}), 83.4 (C-1), 80.7, 78.9, 76.5 (C-3, 4, 5), 75.5 (C-5′), 73.2 (C-2′), 72.9 (C-2), 70.5 (C-4′), 69.6, 69.2, 68.7, 68.2 (C_{Cp}), 68.1 (C-3′), 60.6 (C-6), 60.4 (C-6′), 27.9 ppm (CH_2S); IR (KBr): $\tilde{\nu}$ = 3396, 2895, 1084, 1036 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{36}H_{54}O_{20}S_2Fe$: 926.1999; found: 949.1901 $[M+Na]^+$

General procedure for the synthesis of the azido-ferrocene derivatives 18 and 19: A solution of ferrocene derivative **1** (50 mg, 0.231 mmol) or **8** (50 mg, 0.203 mmol) and sodium azide (6 equiv per hydroxyl group) in glacial acetic acid (3 mL) was stirred at 50°C for 3 h. The reaction mixture was diluted in CH_2Cl_2 (50 mL) and the organic phase was washed with a saturated solution of $NaHCO_3$ (3×50 mL), dried (Na_2SO_4), filtered and evaporated under vacuum. The crude was purified by column chromatography.

Azidomethylferrocene (18): Column chromatography (EtOAc/hexane 1:25) gave **18** (51 mg, 92%) as a dark red oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.23 (m, 2H; H_{Cp}), 4.19 (m, 2H; H_{Cp}), 4.16 (brs, 5H; $H_{Cp'}$), 4.11 ppm (brs, 2H; CH_2N_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 82.2 (C_{ipso}), 68.8 (C_{Cp} $C_{Cp'}$), 68.6 (C_{Cp}), 51.0 ppm (CH_2N_3); IR (Film): $\tilde{\nu}$ = 3093, 2922, 2853, 2090 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{11}H_{11}N_3Fe$: 241.0302; found: 241.0302 $[M]^+$.

1,1′-Bis(azidomethyl)ferrocene (19): Column chromatography (diethyl ether/hexane 1:3) gave **19** (57 mg, 95%) as a dark red oil: ^{1}H NMR (300 MHz, $CDCl_3$): δ = 4.22 (m, 2H; H_{Cp}), 4.20 (m, 2H; H_{Cp}), 4.11 ppm (brs, 4H; CH_2N_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 80.2 (C_{ipso}), 69.5 (C_{Cp}), 69,3 (C_{Cp}), 50.7 ppm (CH_2N_3); IR (Film): $\tilde{\nu}$ = 2967, 2921, 2852, 2085 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{12}H_{12}N_6Fe$: 296.0473; found: 296.0473 $[M]^+$.

General procedure for the synthesis of 1,2,3-triazole derivatives: $(EtO)_3P{\cdot}CuI$ (0.2 equiv per azido group) was added to a solution of azido-ferrocene derivative **18** or **19** or 1-ethynylferrocene **29** and propargyl glycoside **20**–**22** (1.1 equiv per azido group) or 2-azidoethyl glycoside **30**–**31** (1.1 equiv) in dry toluene (6 mL). The mixture was stirred under reflux for 45 min. The solvent was removed by evaporation under vacuum and the crude was purified by column chromatography to yield the corresponding 1,2,3-triazole derivative.

[4-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methylferrocene (23): Starting from **18** (40 mg, 0.166 mmol), column chromatography (EtOAc/hexane 2:1) gave **23** (99 mg, 95%) as a yellow solid. M.p. 51°C; $[\alpha]_D^{25} = -24$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.43 (s, 1H; H-5-C_2HN_3), 5.30 (s, 2H; CH_2N), 5.18 (t, ^3J = 9.4 Hz, 1H; H-3), 5.08 (t, ^3J = 9.6 Hz, 1H; H-4), 4.98 (t, ^3J = 8.7 Hz, 1H; H-2), 4.88 (d, ^2J = 12.7 Hz, 1H; CHO), 4.79 (d, ^2J = 12.7 Hz, 1H; CH_2O), 4.66 (d, ^3J(H1,H2) = 8.0 Hz, 1H; H-1), 4.28 (t, ^3J = 1.8 Hz, 2H; H_{Cp}), 4.26 (dd, ^2J(H6,H6′) = 12.5 Hz, ^3J(H5,H6) = 4.8 Hz, 1H; H-6), 4.22 (t, ^3J = 1.8 Hz, 2H; H_{Cp}), 4.20 (s, 5H; $H_{Cp'}$), 4.12 (dd, ^2J(H6,H6′) = 12.4 Hz, ^3J(H5,H6′) = 2.3 Hz, 1H; H-6′), 3.71 (ddd, ^3J(H4,H5) = 9.8 Hz, ^3J-(H5,H6) = 4.7 Hz, ^3J(H5,H6′) = 2.4 Hz, 1H; H-5), 2.08 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 1.99 (s, 3H; CH_3CO), 1.89 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.1, 169.4 (CO), 144.0 (C-4-C_2HN_3), 122.1 (C-5-C_2HN_3), 99.7 (C-1), 80.6 (C_{ipso}), 72.8 (C-3), 71.8 (C-5), 71.2 (C-2), 69.1, 68.9 (C_{Cp}, $C_{Cp'}$), 68.3 (C-4), 62.9 (CH_2O), 61.8 (C-6), 50.1 (CH_2N), 20.7, 20.6, 20.5 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2952, 2922, 1750, 1373, 1224, 1039 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{28}H_{33}O_{10}N_3Fe$: 627.1515; found: 650.1410 $[M+Na]^+$.

[4-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methylferrocene (24): Starting from **18** (50 mg, 0.207 mmol), column chromatography (EtOAc/hexane 2:1) gave **24** (127 mg, 98%) as a yellow solid. M.p. 44–45°C; $[\alpha]_D^{25} = +32$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.48 (s, 1H; H-5-C_2HN_3), 5.30–5.22 (m, 5H; CH_2N, H-2,3,4), 4.93 (s, 1H; H-1), 4.78 (d, ^2J = 12.2 Hz, 1H; CHO), 4.64 (d, ^2J = 12.2 Hz, 1H; CHO), 4.32 (brs, 2H; H_{Cp}), 4.29–4.16 (m, 2H; H-5,6), 4.24 (brs, 2H; H_{Cp}), 4.21 (s, 5H; $H_{Cp'}$), 4.05 (brd, ^2J(H6,H6′) = 12.0 Hz, 1H; H-6′), 2.14 (s, 3H; CH_3CO), 2.10 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 1.97 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 169.8 (CO), 143.3 (C-4-C_2HN_3), 122.3 (C-5-C_2HN_3), 96.9 (C-1), 80.7 (C_{ipso}), 69.4, 69.3, 69.1, 68.7 (C-2, 3, 5, C_{Cp}), 69.0 ($C_{Cp'}$), 66.1 (C-4), 62.3 (CH_2O), 61.1 (C-6), 50.2 (CH_2N), 20.9, 20.8, 20.7 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2934, 1748, 1370, 1225, 1046 cm^{-1}; HRMS (FAB): *m/z* calcd for $C_{28}H_{33}O_{10}N_3Fe$: 627.1515; found: 650.1411 $[M+Na]^+$.

{4-[2,3,6-Tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazol-1-yl}methylferrocene (25): Starting from **18** (50 mg, 0.207 mmol), column chromatography (EtOAc/hexane 2:1) gave **25** (189 mg, 99%) as a yellow solid. M.p. 89°C (decomp); $[\alpha]_D^{25} = -16$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.39 (s, 1H; H-5-C_2HN_3), 5.31 (d, ^3J = 2.5 Hz, 1H; H-4′), 5.27 (brs, 2H; CH_2N), 5.13 (t, ^3J = 9.3 Hz, 1H; H-3), 5.07 (dd, ^3J(H2′,H3′) = 10.4 Hz, ^3J-(H1′,H2′) = 7.9 Hz, 1H; H-2′), 4.92 (dd, ^3J(H2′,H3′) = 10.4 Hz, ^3J-(H3′,H4′) = 3.5 Hz, 1H; H-3′), 4.85 (t, ^3J = 8.7 Hz, 1H; H-2), 4.82 (brd, ^2J = 13.2 Hz, 1H; CHO), 4.73 (brd, ^2J = 13.2 Hz, 1H; CHO), 4.57 (d, ^3J-(H1,H2) = 7.9 Hz, 1H; H-1), 4.45 (dd, ^2J(H6,H6) = 11.8 Hz, ^3J(H5,H6) = 1.6 Hz, 1H; H-6), 4.44 (d, ^3J(H1′,H2′) = 7.7 Hz, 1H; H-1′), 4.26 (t, ^3J = 1.7 Hz, 2H; H_{Cp}), 4.18 (dd, ^3J = 3.5 Hz, ^3J = 1.7 Hz, 2H; H_{Cp}), 4.56 (brs, 5H; $H_{Cp'}$), 4.13–4.01 (m, 3H; H-6,6′,6′), 3.84 (t, ^3J = 7.0 Hz, 1H; H-5′), 3.76 (t, ^3J = 9.5 Hz, 1H; H-4), 3.58 (dd, ^3J = 9.9 Hz, ^3J = 3.2 Hz, 1H; H-5), 2.12 (s, 3H; CH_3CO), 2.09 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 2.01 (s, 6H; CH_3CO), 1.99 (s, 3H; CH_3CO), 1.93 (s, 3H; CH_3CO), 1.87 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.3, 170.2, 170.1, 170.0, 169.6, 169.5, 168.9 (CO), 143.9 (C-4-C_2HN_3), 122.0 (C-5-C_2HN_3), 100.9 (C-1′), 99.3 (C-1), 80.5 (C_{ipso}), 76.0 (C-4), 72.6 (C-3, 5), 71.4 (C-2), 70.9 (C-3′), 70.6 (C-5′), 69.1 (C-2′), 69.0, 68.9 (C_{Cp}), 68.8 ($C_{Cp'}$), 66.5 (C-4′), 62.7 (CH_2O), 61.8 (C-6), 60.7 (C-6′), 50.0 (CH_2N), 20.8, 20.7, 20.6, 20.5, 20.4 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2954, 2925, 1751, 1371, 1230, 1051 cm^{-1}; MS (ES-TOF): *m/z* calcd for $C_{40}H_{49}O_{18}N_3Fe$: 915.2361; found: 916.2423 $[M+H]^+$.

1,1′-Bis{[4-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl}ferrocene (26): Starting from **19** (55 mg, 0.186 mmol), column chromatography (EtOAc/hexane 4:1→6:1) gave **26** (176 mg, 88%) as a yellow solid. M.p. 84–87°C; $[\alpha]_D^{25} = -26$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.51 (s, 2H; H-5-C_2HN_3), 5.26 (s, 4H; CH_2N), 5.19 (t, ^3J = 9.4 Hz, 2H; H-3), 5.08 (t, ^3J = 9.6 Hz, 2H; H-4), 4.98 (t, ^3J = 8.7 Hz, 2H; H-2), 4.92 (d, ^2J = 12.6 Hz, 2H; CHO), 4.79 (d, ^2J = 12.5 Hz, 2H; CHO), 4.68 (d, ^3J(H1,H2) = 7.9 Hz, 2H; H-1), 4.28 (brs, 4H; H_{Cp}), 4.23 (brs, 6H; H_{Cp}, H-6), 4.14 (dd, ^2J(H6,H6′) = 12.2 Hz, ^3J(H5,H6′) = 2.2 Hz, 2H; H-6′), 3.74 (ddd, ^3J(H4,H5) = 9.7 Hz, ^3J-(H5,H6) = 4.0 Hz, ^3J(H5,H6′) = 2.2 Hz, 2H; H-5), 2.08 (s, 6H; CH_3CO), 2.02 (s, 6H; CH_3CO), 1.98 (s, 6H; CH_3CO), 1.91 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.0, 169.3, 169.2 (CO), 144.1 (C-4-C_2HN_3), 122.5 (C-5-C_2HN_3), 99.9 (C-1), 82.3 (C_{ipso}), 72.7 (C-3), 71.8 (C-5), 71.1 (C-2), 69.9, 69.8, 69.6, 69.4 (C_{Cp}), 68.3 (C-4), 69.2 (CH_2O), 61.7 (C-6), 49.4 (CH_2N), 20.7, 20.6, 20.5 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2954, 2853, 1753, 1371, 1226, 1041 cm^{-1}; MS (MALDI-TOF): *m/z* calcd for $C_{46}H_{56}O_{20}N_6Fe$: 1068.290; found: 1068.171 $[M]^+$, 1069.184 $[M+H]^+$, 1091.285 $[M+Na]^+$.

1,1′-Bis{[4-(2,3,4,6-tetra-*O*-acetyl-α-D-mannopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl}ferrocene (27): Starting from **19** (50 mg, 0.169 mmol), column chromatography (EtOAc/hexane 10:1) gave **27** (171 mg, 94%) as a yellow solid. M.p. 78–81°C; $[\alpha]_D^{25} = +39$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 2H; H-5-C_2HN_3), 5.30–5.29 (m, 8H; CH_2N, H-2,4), 5.22 (brs, 2H; H-3), 4.95 (s, 2H; H-1), 4.82 (d, ^2J = 12.3 Hz, 2H; CHO), 4.66 (d, ^2J = 12.3 Hz, 2H; CHO), 4.31 (brs,

4H; H_{Cp}), 4.30–4.25 (m, 6H; H_{Cp}, H-6), 4.13–4.03 (m, 4H; H-5,6′), 2.14 (s, 6H; CH_3COO), 2.11 (s, 6H; CH_3CO), 2.03 (s, 6H; CH_3CO), 1.97 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.0, 169.7 (CO), 143.5 (C-4-C_2HN_3), 122.6 (C-5-C_2HN_3), 97.0 (C-1), 82.2 (C_{ipso}), 70.1, 69.7 (C_{Cp}), 69.5, 69.1, 68.7 (C-2, 3, 5), 66.1 (C-4), 62.4 (CH_2O), 61.1 (C-6), 49.7 (CH_2N), 20.9, 20.8, 20.7 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2933, 1749, 1370, 1225, 1046 cm^{-1}; MS (MALDI-TOF): *m*/*z* calcd for $C_{46}H_{56}O_{20}N_6Fe$: 1068.290; found: 1091.277 $[M+Na]^+$.

1,1′-Bis({4-[2,3,6-Tri-*O*-acetyl-4-*O*-(2′,3′,4′,6′-tetra-*O*-acetyl-β-D-galactopyranosyl)-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazol-1-yl}methyl)ferrocene (28): Starting from **19** (60 mg, 0.203 mmol), column chromatography (EtOAc/MeOH 10:1) gave **28** (329 mg, 99%) as a yellow solid. M.p. 118°C (decomp); $[\alpha]_D^{25} = -13$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.46 (s, 2H; H-5-C_2HN_3), 5.32 (d, ^3J = 3.2 Hz, 2H; H-4′), 5.24 (brs, 4H; CH_2N), 5.14 (t, ^3J = 9.5 Hz, 2H; H-3), 5.08 (dd, ^3J(H2′,H3′) = 10.5 Hz, ^3J(H1′,H2′) = 8.1 Hz, 2H; H-2′), 4.93 (dd, ^3J(H2′,H3′) = 10.5 Hz, ^3J(H3′,H4′) = 3.2 Hz, 2H; H-3′), 4.87 (d, ^2J = 12.6 Hz, 2H; CHO), 4.85 (brd, ^3J = 8.9 Hz, 2H; H-2), 4.76 (d, ^2J = 12.5 Hz, 2H; CHO), 4.59 (d, ^3J-(H1,H2) = 7.9 Hz, 2H; H-1), 4.50 (brd, ^2J(H6,H6) = 11.9 Hz, 2H; H-6), 4.46 (d, ^3J(H1′,H2′) = 7.9 Hz, 2H; H-1′), 4.26 (brs, 2H; H_{Cp}), 4.21 (brs, 6H; H_{Cp}), 4.14–4.02 (m, 6H; H-6,6′,6′), 3.85 (t, ^3J = 6.8 Hz, 2H; H-5′), 3.78 (t, ^3J = 9.3 Hz, 2H; H-4), 3.61 (dd, ^3J = 9.5 Hz, ^3J = 3.1 Hz, 2H; H-5), 2.15 (s, 6H; CH_3CO), 2.13 (s, 6H; CH_3CO), 2.03 (s, 6H; CH_3CO), 2.02 (s, 6H; CH_3CO), 2.00 (s, 6H; CH_3CO), 1.94 (s, 6H; CH_3CO), 1.90 ppm (s, 6H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.2, 170.0, 169.9, 169.6, 169.5, 168.9 (CO), 144.0 (C-4-C_2HN_3), 122.4 (C-5-C_2HN_3), 100.8 (C-1′), 99.6 (C-1), 82.1 (C_{ipso}), 75.9 (C-4), 72.6 (C-5), 72.5 (C-3), 71.3 (C-2), 70.8 (C-3′), 70.5 (C-5′), 69.9, 69.8, 69.6, 69.4 (C_{Cp}), 68.9 (C-2′), 66.5 (C-4′), 62.9 (CH_2O), 61.7 (C-6), 60.6 (C-6′), 49.4 (CH_2N), 20.9, 20.7, 20.6, 20.5, 20.4 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2957, 1751, 1371, 1228, 1049 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{70}H_{88}O_{36}N_6Fe$: 1644.4589; found: 1645.4564 $[M+H]^+$.

[1-(2,3,4,6-Tetra-*O*-acetyl-β-D-glucopyranosyloxyethyl)-1*H*-1,2,3-triazol-4-yl]ferrocene (32): Starting from **29** (20 mg, 0.095 mmol), column chromatography (EtOAc/hexane 2:1) gave **32** (57 mg, 95%) as an orange solid. M.p. 182–185°C; $[\alpha]_D^{25} = -56$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.54 (s, 1H; H-5-C_2HN_3), 5.18 (t, ^3J = 9.4 Hz, 1H; H-3), 5.07 (t, ^3J = 9.5 Hz, 1H; H-4), 5.03 (t, ^3J = 8.7 Hz, 1H; H-2), 4.82 (brs, 1H; H_{Cp}), 4.68 (brs, 1H; H_{Cp}), 4.68–4.60 (m, 1H; CHN), 4.52 (ddd, ^2J = 14.5 Hz, ^3J = 8.4 Hz, ^3J = 3.5 Hz, 1H; CHN), 4.47 (d, ^3J(H1,H2) = 7.7 Hz, 1H; H-1), 4.29 (brs, 2H; H_{Cp}), 4.29–4.22 (m, 2H; H-6, CHO), 4.14 (dd, ^2J(H6,H6′) = 12.6 Hz, ^3J(H5,H6′) = 2.4 Hz, 1H; H-6′), 4.09 (brs, 5H; $H_{Cp'}$), 3.90 (m, ^3J = 3.3 Hz, 1H; CHO), 3.70 (ddd, ^3J(H4,H5) = 9.8 Hz, ^3J-(H5,H6) = 4.7 Hz, ^3J(H5,H6′) = 2.3 Hz, 1H; H-5), 2.08 (s, 3H; CH_3CO), 2.02 (s, 3H; CH_3CO), 1.99 (s, 3H; CH_3CO), 1.84 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 169.5, 169.4 (CO), 146.8 (C-4-C_2HN_3), 120.5 (C-5-C_2HN_3), 100.6 (C-1), 75.5 (C_{ipso}), 72.5 (C-3), 72.1 (C-2), 71.0 (C-5), 69.6 ($C_{Cp'}$), 68.7 (C_{Cp}), 68.6 (C_{Cp}), 68.3 (C-4), 67.9 (CH_2O), 66.7 (C_{Cp}), 66.6 (C_{Cp}), 61.8 (C-6), 50.0 (CH_2N), 20.8, 20.6 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2953, 1750, 1372, 1228, 1037 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{28}H_{33}O_{10}N_3Fe$: 627.1515; found: 650.1420 $[M+Na]^+$.

[1-(2,3,4,6-Tetra-*O*-acetyl-α-D-mannopyranosyloxyethyl)-1*H*-1,2,3-triazol-4-yl]ferrocene (33): Starting from **29** (50 mg, 0.238 mmol), column chromatography (EtOAc/hexane 2:1) gave **33** (146 mg, 98%) as an orange solid. M.p. 64–68°C; $[\alpha]_D^{25} = -13$ (*c* = 1 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.64 (s, 1H; H-5-C_2HN_3), 5.26 (brs, 3H; H-2,3,4), 4.84 (s, 1H; H-1), 4.80 (brs, 1H; H_{Cp}), 4.74 (brs, 1H; H_{Cp}), 4.61 (m, 2H; CH_2N), 4.29 (brs, 2H; H_{Cp}), 4.20–4.11 (m, 1H; CHO), 4.16 (dd, ^2J(H6,H6′) = 12.2 Hz, ^3J(H5,H6) = 4.9 Hz, 1H; H-6), 4.07 (brs, 5H; $H_{Cp'}$), 3.99 (dd, ^2J-(H6,H6′) = 12.3 Hz, ^3J(H5,H6′) = 2.1 Hz, 1H; H-6′), 3.87 (ddd, ^2J = 9.7 Hz, ^3J = 4.2 Hz, ^3J = 4.2 Hz, 1H; CHO), 3.43 (brs, 1H; H-5), 2.14 (s, 3H; CH_3CO), 2.08 (s, 3H; CH_3CO), 2.01 (s, 3H; CH_3CO), 1.88 ppm (s, 3H; CH_3CO); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.5, 170.0, 169.7 (CO), 147.1 (C-4-C_2HN_3), 120.1 (C-5-C_2HN_3), 97.4 (C-1), 75.4 (C_{ipso}), 69.7 ($C_{Cp'}$), 69.3, 69.1, 68.9 (C-2, 3, 5), 68.7 (C_{Cp}), 66.8 (C_{Cp}), 66.2 (CH_2O), 65.6 (C-4), 62.2 (C-6), 49.7 (CH_2N), 20.9, 20.8, 20.7, 20.6 ppm (CH_3CO); IR (KBr): $\tilde{\nu}$ = 2954, 2852, 1748, 1370, 1224, 1046 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{28}H_{33}O_{10}N_3Fe$: 627.1515; found: 650.1414 $[M+Na]^+$.

General procedure for the Zemplén de-*O*-acetylation of 1,2,3-triazol derivatives 23–28 and 32–33: A solution of 1,2,3-triazol derivative **23**–**28** or **32**–**33** in dry MeOH (15–20 mL) or in a mixture of dry MeOH and dry CH_2Cl_2 10:1 (15–20 mL) was made alkaline to pH 9–10 (indicator paper) with a fresh solution of NaOMe in methanol (1M) and stirred at room temperature for 2–24 h following the reaction by TLC. If the product precipitated, the solvent was concentrated under vacuum to 1–2 mL and diethyl ether was added. The solid was filtered off and washed with diethyl ether. In other cases, the solvent was removed under vacuum and the crude was purified by column chromatography. The pure compound was dissolved in water and lyophilised.

[4-(β-D-Glucopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methylferrocene (34): Starting from **23** (306 mg, 0.488 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 3:2) gave **34** (213 mg, 95%) as a yellow solid. M.p. 65–66°C; $[\alpha]_D^{25} = -22$ (*c* = 0.25 in MeOH); ^{1}H NMR (300 MHz, D_2O, 60°C): δ = 8.39 (s, 1H; H-5-C_2HN_3), 5.72 (s, 2H; CH_2N), 5.30 (d, ^2J = 12.8 Hz, 1H; CHO), 5.22 (d, ^2J = 12.6 Hz, 1H; CHO), 4.86 (d, ^3J-(H1,H2) = 8.1 Hz, 1H; H-1), 4.75 (t, ^3J = 1.3 Hz, 2H; H_{Cp}), 4.66 (t, ^3J = 1.3 Hz, 2H; H_{Cp}), 4.61 (brs, 5H; $H_{Cp'}$), 4.21 (dd, ^2J(H6,H6′) = 12.5 Hz, ^3J-(H5,H6) = 1.5 Hz, 1H; H-6), 4.05 (dd, ^2J(H6,H6′) = 12.5 Hz, ^3J(H5,H6′) = 5.3 Hz, 1H; H-6′), 3.82 (t, ^3J = 9.1 Hz, 1H; H-3), 3.74 (m, 1H; H-4), 3.70 (t, ^3J = 1.5 Hz, 1H; H-5), 3.64 ppm (t, ^3J = 8.3 Hz, 1H; H-2); ^{13}C NMR (75 MHz, D_2O, 60°C): δ = 144.1 (C-4-C_2HN_3), 125.3 (C-5-C_2HN_3), 101.9 (C-1), 82.2 (C_{ipso}), 76.4 (C-5), 76.3 (C-3), 73.5 (C-2), 70.1 (C-4), 69.4 (C_{Cp}, $C_{Cp'}$), 69.2 (C_{Cp}), 62.4 (CH_2O), 61.3 (C-6), 50.2 ppm (CH_2N); IR (KBr): $\tilde{\nu}$ = 3379, 2883, 1059, 1022 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{25}O_6N_3Fe$: 459.1093; found: 482.0990 $[M+Na]^+$.

[4-(α-D-Mannopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methylferrocene (35): Starting from **24** (201 mg, 0.320 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 3:2) gave **35** (139 mg, 95%) as a yellow solid. M.p. 65–67°C; $[\alpha]_D^{25} = +56$ (*c* = 0.25 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.94 (s, 1H; H-5-C_2HN_3), 5.34 (s, 2H; CH_2N), 4.85 (d, ^3J(H1,H2) = 10.1 Hz, 1H; H-1), 4.76 (d, ^2J = 12.3 Hz, 1H; CHO), 4.61 (d, ^2J = 12.3 Hz, 1H; CHO), 4.34 (d, ^3J = 1.6 Hz, 2H; H_{Cp}), 4.22 (t, ^3J = 1.7 Hz, 2H; H_{Cp}), 4.19 (s, 5H; $H_{Cp'}$), 3.82 (d, ^2J(H6,H6′) = 11.7 Hz, 1H; H-6), 3.77 (brs, 1H; H-2), 3.70 (dd, ^2J(H6,H6′) = 12.1 Hz, ^3J-(H5,H6′) = 5.6 Hz, 1H; H-6′), 3.64 (brd, ^3J = 3.7 Hz, 1H; H-3), 3.60 (t, ^3J = 9.1 Hz, 1H; H-4), 3.56–3.52 ppm (m, 1H; H-5); ^{13}C NMR (75 MHz, CD_3OD): δ = 145.2 (C-4-C_2HN_3), 124.8 (C-5-C_2HN_3), 100.8 (C-1), 83.0 (C_{ipso}), 74.9 (C-5), 72.5 (C-3), 72.0 (C-2), 69.9 (C_{Cp}), 69.8 (C_{Cp}, $C_{Cp'}$), 68.6 (C-4), 62.9 (C-6), 60.7 (CH_2O), 51.0 ppm (CH_2N); IR (KBr): $\tilde{\nu}$ = 3398, 2923, 1053 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{20}H_{25}O_6N_3Fe$: 459.1093; found: 482.0989 $[M+Na]^+$.

{4-[4-*O*-(β-D-Galactopyranosyl)-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazol-1-yl}methylferrocene (36): Starting from **25** (169 mg, 0.185 mmol) in dry MeOH/CH_2Cl_2 10:1, column chromatography (EtOAc/MeOH 2:1 → −8 (*c* = 1 in MeOH); ^{1}H NMR (300 MHz, CD_3OD): δ = 7.95 (s, 1H; H-5-C_2HN_3), 5.34 (s, 2H; CH_2N), 4.93 (d, ^2J = 12.5 Hz, 1H; CHO), 4.75 (d, ^2J = 12.5 Hz, 1H; CHO), 4.40 (d, ^3J(H1,H2) = 7.8 Hz, 1H; H-1), 4.35 (d, ^3J(H1′,H2′) = 5.6 Hz, 1H; H-1′), 4.34 (brd, ^3J = 1.6 Hz, 2H; H_{Cp}), 4.21 (dd, ^3J = 3.5 Hz, ^3J = 1.7 Hz, 2H; H_{Cp}), 4.20 (s, 5H; $H_{Cp'}$), 3.92 (dd, ^2J-(H6,H6) = 12.1 Hz, ^3J(H5,H6) = 2.5 Hz, 1H; H-6), 3.83 (dd, ^2J(H6,H6) = 12.1 Hz, ^3J(H5,H6) = 4.1 Hz, 1H; H-6), 3.81 (brs, 1H; H-4′), 3.78 (dd, ^2J-(H6′,H6′) = 11.5 Hz, ^3J(H5′,H6′) = 7.6 Hz, 1H; H-6′), 3.69 (dd, ^2J-(H6′,H6′) = 11.3 Hz, ^3J(H5′,H6′) = 4.7 Hz, 1H; H-6′), 3.60–3.58 (m, 1H; H-5′), 3.57 (t, ^3J = 8.7 Hz, 1H; H-4), 3.51 (t, ^3J = 8.6 Hz, 1H; H-3), 3.50 (dd, ^3J(H1′,H2′) = 5.4 Hz, ^3J(H2′,H3′) = 3.3 Hz, 1H; H-2′), 3.45 (dd, ^3J-(H3′,H4′) = 6.0 Hz, ^3J(H2′,H3′) = 3.5 Hz, 1H; H-3′), 3.42–3.39 (m, 1H; H-5), 3.21 ppm (t, ^3J = 8.4 Hz, 1H; H-2); ^{13}C NMR (75 MHz, CD_3OD): δ = 145.6 (C-4-C_2HN_3), 124.8 (C-5-C_2NH_3), 105.1 (C-1′), 103.4 (C-1), 83.0 (C_{ipso}), 80.5 (C-4), 77.1 (C-5′), 76.5 (C-5), 76.3 (C-3), 74.8 (C-3′), 74.6 (C-2), 72.5 (C-2′), 70.3 (C-4′), 69.9 (C_{Cp}, $C_{Cp'}$), 63.1 (CH_2O), 62.5 (C-6′), 61.9 (C-6), 51.1 ppm (CH_2N); IR (KBr): $\tilde{\nu}$ = 3391, 2922, 2855, 1057, 1023 cm^{-1}; HRMS (FAB): *m*/*z* calcd for $C_{26}H_{35}O_{11}N_3Fe$: 621.1621; found: 621.1616 $[M]^+$, 622.1699 $[M+H]^+$.

1,1′-Bis{[4-(β-D-glucopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl}ferrocene (37): Starting from **26** (162 mg, 0.152 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 2:1 → 1:1) gave **37** (103 mg,

93%) as a yellow solid. M.p. 87–88°C; $[\alpha]_D^{25}=-28$ ($c=0.25$ in MeOH); ^{1}H NMR (300 MHz, D_2O, 60°C): $\delta=8.39$ (s, 2H; H-5-C_2HN_3), 5.69 (s, 4H; CH_2N), 5.31 (d, $^2J=12.6$ Hz, 2H; CHO), 5.22 (d, $^2J=12.7$ Hz, 2H; CHO), 4.89 (d, ^3J(H1,H2)=8.1 Hz, 2H; H-1), 4.72 (s; H_{Cp}, HDO), 4.66 (brs, 4H; H_{Cp}), 4.22 (dd, ^2J(H6,H6′)=12.3 Hz, ^3J(H5,H6)=1.4 Hz, 2H; H-6), 4.06 (dd, ^2J(H6,H6′)=12.3 Hz, ^3J(H5,H6′)=5.0 Hz, 2H; H-6′), 3.83 (t, $^3J=8.8$ Hz, 2H; H-3), 3.76 (brs, 2H; H-4), 3.71 (dd, ^3J(H4,H5)=1.9 Hz, ^3J(H5,H6)=1.5 Hz, 2H; H-5), 3.64 ppm (t, $^3J=8.4$ Hz, 2H; H-2); ^{13}C NMR (75 MHz, D_2O, 60°C): $\delta=144.2$ (C-4-C_2HN_3), 125.3 (C-5-C_2HN_3), 102.0 (C-1), 82.9 (C_{ipso}), 76.4 (C-5), 76.3 (C-2), 73.5 (C-3), 70.3 (C_{Cp}), 70.1 (C-4), 70.0 (C_{Cp}), 62.4 (CH_2O), 61.3 (C-6), 49.9 ppm (CH_2N); IR (KBr): $\tilde{\nu}=3404$, 2923, 2883, 1052 cm^{-1}; HRMS (FAB): m/z calcd for $C_{30}H_{40}O_{12}N_6Fe$: 732.2054; found: 755.1941 $[M+Na]^+$.

1,1′-Bis{[4-(α-D-mannopyranosyloxymethyl)-1*H*-1,2,3-triazol-1-yl]methyl}ferrocene (38): Starting from **27** (168 mg, 0.157 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 2:1→1:1) gave **38** (101 mg, 88%) as a yellow solid. M.p. 102–103°C; $[\alpha]_D^{25}=+68$ ($c=0.25$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta=7.99$ (s, 2H; H-5-C_2HN_3), 5.33 (brs, 4H; CH_2N), 4.87 (d, ^3J(H1,H2)=8.8 Hz, 2H; H-1), 4.78 (d, $^2J=12.5$ Hz, 2H; CHO), 4.63 (d, $^2J=12.3$ Hz, 2H; CHO), 4.35 (brs, 4H; H_{Cp}), 4.24 (brs, 4H; H_{Cp}), 3.83 (brd, ^2J(H6,H6′)=11.1 Hz, 2H; H-6), 3.78 (brs, 2H; H-2), 3.71 (dd, ^2J(H6,H6′)=11.1 Hz, ^3J(H5,H6′)=5.3 Hz, 2H; H-6′), 3.66 (brs, 2H; H-3), 3.62 (t, $^3J=9.1$ Hz, 2H; H-4), 3.58–3.53 ppm (m, 2H; H-5); ^{13}C NMR (75 MHz, CD_3OD): $\delta=145.2$ (C-4-C_2HN_3), 125.1 (C-5-C_2HN_3), 100.7 (C-1), 84.1 (C_{ipso}), 74.9 (C-5), 72.4 (C-3), 71.9 (C-2), 70.9 (C_{Cp}), 70.8 (C_{Cp}), 68.5 (C-4), 62.9 (C-6), 60.7 (CH_2O), 50.6 ppm (CH_2N); IR (KBr): $\tilde{\nu}=3409$, 2926, 1058 cm^{-1}; HRMS (FAB): m/z calcd for $C_{30}H_{40}O_{12}N_6Fe$: 732.2054; found: 755.1942 $[M+Na]^+$.

1,1′-Bis({4-[4-*O*-(β-D-galactopyranosyl)-β-D-glucopyranosyloxymethyl]-1*H*-1,2,3-triazol-1-yl}methyl)ferrocene (39): Starting from **28** (314 mg, 0.191 mmol) in dry MeOH/CH_2Cl_2 10:1, precipitation with diethyl ether gave **39** (185 mg, 92%) as a yellow solid. M.p. 202°C (decomp); $[\alpha]_D^{25}=-12$ ($c=1$ in H_2O); ^{1}H RMN (300 MHz, [D$_6$]DMSO): $\delta=8.08$ (s, 2H; H-5-C_2HN_3), 5.33 (s, 4H; CH_2N), 4.82 (d, $^2J=12.2$ Hz, 2H; CHO), 4.61 (d, $^2J=12.2$ Hz, 2H; CHO), 4.38 (t, $^3J=1.7$ Hz, 4H; H_{Cp}), 4.31 (d, ^3J(H1,H2)=7.9 Hz, 2H; H-1), 4.22 (t, $^3J=1.9$ Hz, 4H; H_{Cp}), 4.20 (brs, 2H; H-1′), 3.79 (brd, ^2J(H6,H6)=11.0 Hz, 2H; H-6), 3.62–3.58 (m, 4H; H-3′,6), 3.59–3.45 (m, 6H; H-5′,6′,6′), 3.29 (brs; H-2′,3,4,4′,5, HDO), 3.02 ppm (t, $J=7.5$ Hz, 2H; H-2); ^{13}C RMN (75 MHz, [D$_6$]DMSO): $\delta=$ 143.7 (C-4-C_2HN_3), 123.7 (C-5-C_2NH_3), 103.8 (C-1′), 101.8 (C-1), 83.0 (C_{ipso}), 80.7 (C-4), 75.5 (C-5′), 74.9 (C-3,5), 73.2 (C-2′), 73.0 (C-2), 70.5 (C-4′), 69.6, 69.3 (C_{Cp}), 68.0 (C-3′), 61.7 (CH_2O), 60.5 (C-6), 60.3 (C-6′), 48.6 ppm (CH_2N); IR (KBr): $\tilde{\nu}=3409$, 2873, 1047 cm^{-1}; MS (MALDI-TOF): m/z calcd for $C_{42}H_{60}O_{22}N_6Fe$: 1056.3110; found: 1079.3012 $[M+Na]^+$.

[1-(β-D-Glucopyranosyloxyethyl)-1*H*-1,2,3-triazol-4-yl]ferrocene (40): Starting from **32** (222 mg, 0.354 mmol) in dry MeOH/CH_2Cl_2 10:1, column chromatography (EtOAc/MeOH 2:1) gave **40** (157 mg, 96%) as an orange solid. M.p. 74°C (decomp); $[\alpha]_D^{25}=+4$ ($c=0.25$ in MeOH); ^{1}H NMR (300 MHz, D_2O, 60°C): $\delta=8.45$ (s, 1H; H-5-C_2HN_3), 5.20 (brs, 2H; H_{Cp}), 5.03 (t, $^3J=5.1$ Hz, 2H; CH_2N), 4.84 (brs, 2H; H_{Cp}), 4.80 (d, ^3J(H1,H2)=8.0 Hz, 1H; H-1), 4.65 (dd, $^2J=10.9$ Hz, $^3J=5.1$ Hz, 1H; CHO), 4.56 (s, 5H; $H_{Cp'}$), 4.50 (dd, $^2J=11.3$ Hz, $^3J=5.6$ Hz, 1H; CHO), 4.25 (dd, ^2J(H6,H6′)=12.2 Hz, ^3J(H5,H6)=2.1 Hz, 1H; H-6), 4.06 (dd, ^2J(H6,H6′)=12.2 Hz, ^3J(H5,H6′)=5.6 Hz, 1H; H-6′), 3.84 (t, $^3J=8.9$ Hz, 1H; H-3), 5.77 (dd, ^3J(H5,H6′)=5.6 Hz, ^3J(H5,H6)=2.3 Hz, 1H; H-5), 3.73 (dd, ^3J(H3,H4)=8.4 Hz, ^3J(H4,H5)=1.8 Hz, 1H; H-4), 3.64 ppm (t, $^3J=8.5$ Hz, 1H; H-2); ^{13}C NMR (75 MHz, D_2O, 60°C): $\delta=147.2$ (C-4-C_2HN_3), 122.4 (C-5-C_2HN_3), 102.8 (C-1), 76.4 (C-5), 76.2 (C-3), 74.8 (C_{ipso}), 73.5 (C-2), 70.4 ($C_{Cp'}$), 70.2 (C-4), 69.8 (C_{Cp}), 68.2 (CH_2O), 67.2 (C_{Cp}), 61.4 (C-6), 50.7 ppm (CH_2N); IR (KBr): $\tilde{\nu}=3397$, 2919, 1067, 1040 cm^{-1}; HRMS (FAB): m/z calcd for $C_{20}H_{25}O_6N_3Fe$: 459.1093; found: 482.0996 $[M+Na]^+$.

[1-(α-D-Mannopyranosyloxyethyl-1*H*-1,2,3-triazol-4-yl]ferrocene (41): Starting from **33** (147 mg, 0.234 mmol) in dry MeOH, column chromatography (EtOAc/MeOH 2:1) gave **41** (102 mg, 95%) as an orange solid. M.p. 66°C (decomp); $[\alpha]_D^{25}=+26$ ($c=0.25$ in MeOH); ^{1}H NMR (300 MHz, CD_3OD): $\delta=8.02$ (s, 1H; H-5-C_2HN_3), 4.76 (d, ^3J(H1,H2)=1.4 Hz, 1H; H-1), 4.74 (t, $^3J=1.7$ Hz, 2H; H_{Cp}), 4.66–4.61 (m, 2H; CH_2N), 4.32 (t, $^3J=1.7$ Hz, 2H; H_{Cp}), 4.17 (ddd, $^2J=10.4$ Hz, $^3J=5.9$ Hz, $^3J=4.5$ Hz, 1H; CHO), 4.07 (s, 5H; $H_{Cp'}$), 3.92 (ddd, $^2J=10.7$ Hz, $^3J=$ 6.4 Hz, $^3J=4.5$ Hz, 1H; CHO), 3.82 (dd, ^2J(H6,H6′)=11.7 Hz, ^3J(H5,H6)=2.4 Hz, 1H; H-6) 3.77 (dd, ^3J(H1,H2)=1.7 Hz, ^3J(H2,H3)=3.0 Hz, 1H; H-2), 3.68 (dd, ^2J(H6,H6′)=11.8 Hz, ^3J(H5,H6′)=6.0 Hz, 1H; H-6′), 3.65 (dd, ^3J(H3,H4)=9.2 Hz, ^3J(H2,H3)=3.2 Hz, 1H; H-3), 3.59 (t, $^3J=9.3$ Hz, 1H; H-4), 3.39 ppm (ddd, ^3J(H4,H5)=8.6 Hz, ^3J(H5,H6′)=5.9 Hz, ^3J(H5,H6)=2.1 Hz, 1H; H-5); ^{13}C NMR (75 MHz, CD_3OD): $\delta=148.0$ (C-4-C_2HN_3), 122.0 (C-5-C_2HN_3), 101.7 (C-1), 76.1 (C_{ipso}), 75.0 (C-5), 72.5 (C-3), 71.9 (C-2), 70.6 ($C_{Cp'}$), 69.8 (C_{Cp}), 68.3 (C-4), 67.7 (C_{Cp}), 66.8 (CH_2O), 62.8 (C-6), 51.2 ppm (CH_2N); IR (KBr): $\tilde{\nu}=$ 3404, 2923, 1053 cm^{-1}; HRMS (FAB): m/z calcd for $C_{20}H_{25}O_6N_3Fe$: 459.1093; found: 482.0993 $[M+Na]^+$.

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[16] While performing the electrochemical experiments, we discovered that dilactosyl compound **39** was not pure enough. DPV experiment for **39** showed two oxidation peaks due to the presence of an impurity that we could confirm by HPLC analysis. All attempts carried out by us to purify compound **39** by preparative HPLC failed. We investigated the origin of the impurity and we have concluded that it comes from the synthesis of propargyl lactoside **22**, which was obtained from the reaction of per-*O*-acetyl lactose and propargyl alcohol in the presence of $BF_3{\cdot}OEt_2$ as catalyst (see Experimental Section in ref. [32b]). Under those reaction conditions glycoside **22** is formed together with the α-anomer as a minor product, both anomers having the same R_f value by TLC. The presence of the impurity was not detected by ^1H NMR spectroscopy at first, but a long-time accumulation of a ^{13}C NMR experiment allowed us to observe the presence of the presumably anomeric carbon of the α anomer. However, the synthesis and purification of compound **25** were not affected by the slight impurity of the starting material as it was later confirmed by the electrochemical experiments.

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