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Rotationally Restricted 1,1'-Bis(phenylethynyl) Ferrocene Subunits in Macrocycles

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Abstract

The synthesis of macrocycles comprising a 1,1'-bis(phenylethynyl) ferrocene subunit is developed with the intention to increase the structural control over the spatial arrangement of the two cyclopentadienyl ligands of the ferrocene junction. The target structures were obtained using a modular strategy enabling the assembly of varying ring sizes from a common precursor. In particular macrocycles were either formed by an ether formation or by ring closing metathesis reactions. The macrocycles were obtained in reasonable isolated yields, which allowed their thorough characterization by one- and two-dimensional NMR experiments and in one case, the identity was corroborated by solid-state X-ray diffraction.

Keywords: Metallocenes, ferrocene, macrocycle, (ring-closing) metathesis, bridging strategy

Introduction

The astonishingly versatile organometallic ferrocene (Fc) is a prototype of its kind, first reported in 1951 by Pausen and Kealy.[1] Later on, the structure was deduced due to its reactivity, to be caging the iron(II) ion by negatively charged cyclopentadienyl (Cp) ligands that form a sandwich type motif.[2] Curiosity has spurred rapid achievements in the study of its chemistry. Owing to its three-dimensional structure and its reversible one electron redox behavior, Fc is ubiquitous in chemists' society. For instance, 1,1'-bis(diphenyl-phosphino)ferrocene (DPPF) emerged as a very efficient and sterically adaptable phosphine chelate ligand in palladium-catalyzed amination of aryl halides.[3] Unsymmetrically 1,3-disubstituted ferrocenes have drawn attention as prospects for chiral electro-optical liquid crystal devices[4] and 1,1´-disubstituted phenylethynyl ferrocene structures are dealt as potent molecular wires[5]. A more everyday life application is represented with the 1,1',3-trisubstituted ferrocene derivative of lidocaine, that acts as a redox mediator between the glucose oxidase enzyme and an electrode to monitor glucose levels in the blood of people with diabetes.[6] 1,1'-Diphenylene-ethynylene ferrocene subunits were reported as redox active subunits in molecular rods and have been contacted in molecular junctions.[7] While the rotational freedom between both Cp units usually is an appealing feature of the structure and has been used e.g. as mechanical joint in scissor-type architectures,[8] in molecular rods this flexibility results in a large variety of possible conformations and consequently in a poor structural control. To gain back the control over the subunits spatial arrangement, we became interested in integrating the 1,1'-diphenylene-ethynylene ferrocene subunit into a macrocyclic structure. While the development of a suitable synthetic approach is the main focus of this report, a modular synthetic approach towards a second parallel bridging structure might even provide the tools to vary systematically the angle defined by both diphenylene-ethynylene subunits at the Fc junction.

Here we report three macrocyclic model compounds **1**-**3** comprising 1,1'-diphenylene-ethynylene ferrocene subunits shown in Figure 1. Their syntheses are all based on ring closing reactions forming the second parallel bridge and all three have as common precursor the parent 1,1'-diphenylene-ethylene ferrocene structure comprising an oxybenzyl-4-benzaldehhyde substituent in *ortho*-position of the phenylene ring on both sides (**4**). Thanks to the intramolecular nature of the ring closing reaction, these macrocycles were formed in acceptable yields ranging from 57 to 70%, and were isolated in excellent purity by chromatography.

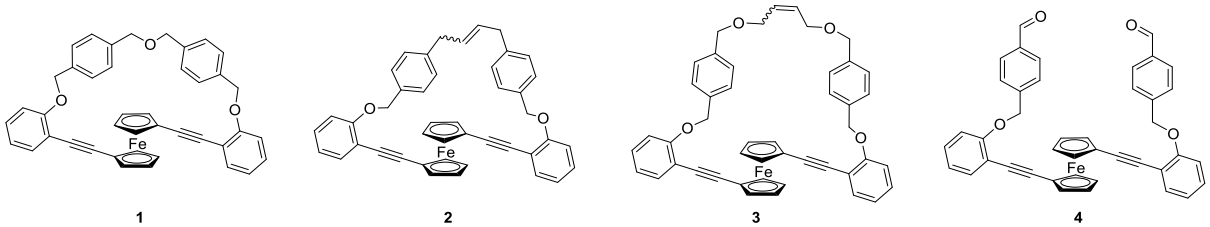
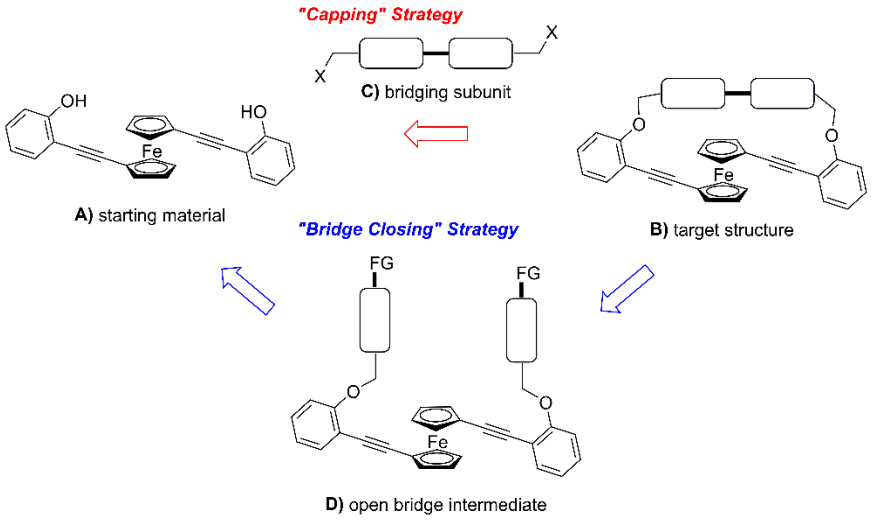


Figure 1: Macrocyclic model compounds **1**-**3** and their precursor **4**.

Synthetic Strategy

The closing of a macrocycle is usually a late step in a synthetic strategy and is often performed in diluted or pseudo diluted conditions to favor the desired intramolecular macrocyclization over intermolecular oligomer- and polymer formation. Exceptions are synthetic strategies profiting either from templates or from particular pre-folded precursors. Here we considered two conceptually different strategies, namely the “capping” approach and the “bridge closing” strategy displayed in Scheme 1. While the “capping” strategy appears considerably more appealing due to the large variety of different bridging structures that might be introduced in a single step, we were exclusively successful with the “bridge closing” strategy so far.



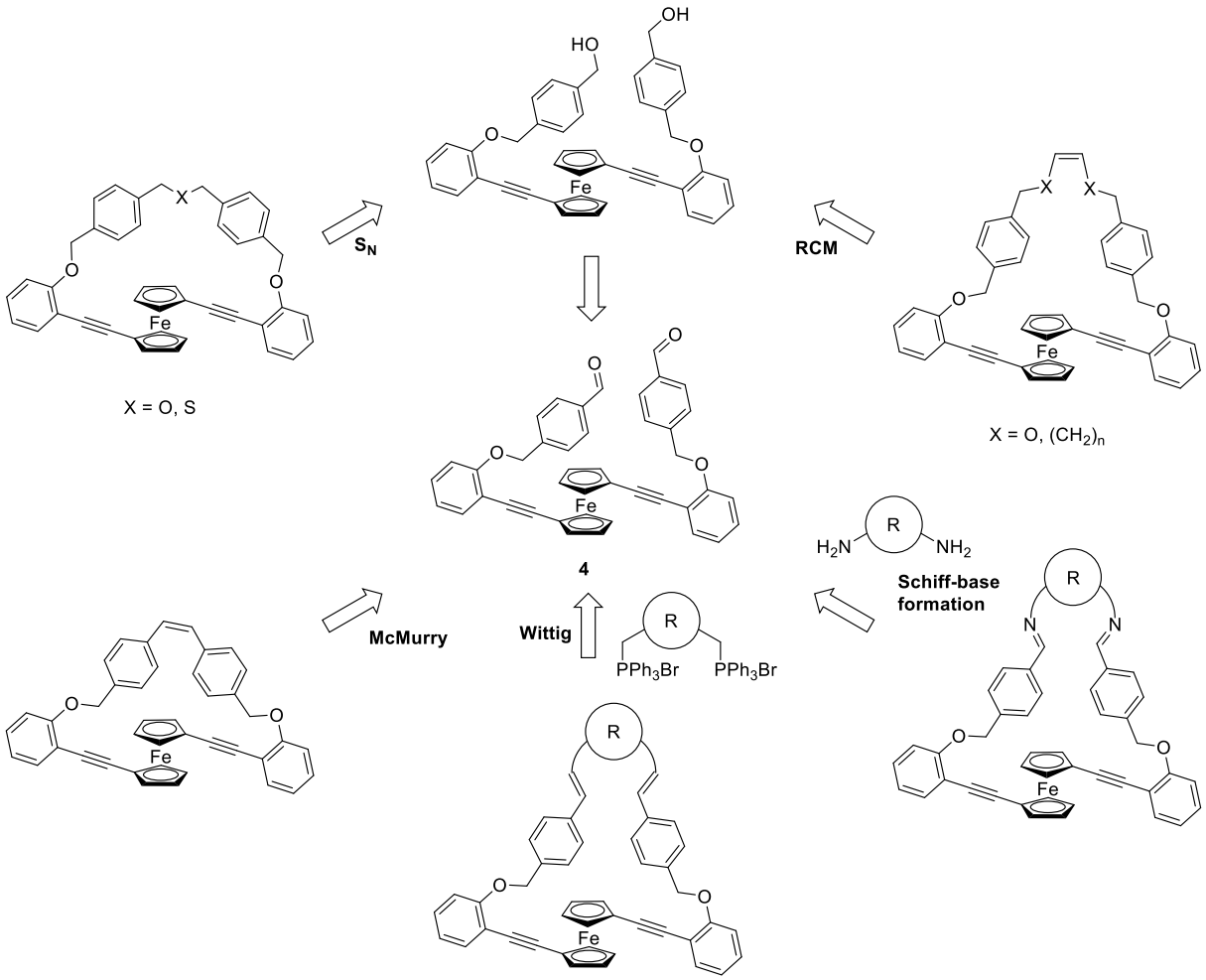
Scheme 1: Assembly of the 1,1’-bis(phenylethynyl)-ferrocene macrocycle based on a disconnection approach following either the “Capping”-Strategy (top: red arrow) or the “Bridge Closing” Strategy (bottom: blue arrows).

Also the “Bridge Closing”-strategy might offer modular diversity in the bridging structure depending on the chemistry selected for the bridge formation. Particular appealing would be an open bridge intermediate (**D** in scheme 1) exposing functional groups giving access to different types of coupling reactions to close the bridge. More important than the increased modularity in the bridging structure is the increased probability to find suitable reactions to close the bridge. Guided by these rational, we chose the benzylic aldehyde precursor **4**, giving access to a broad variety of potential ring closing reactions as displayed in Scheme 2. The precursor **4** exposing two benzaldehyde might be closed directly profiting from an intramolecular *McMurry* type reaction catalyzed by low-valent titanium species.[9]

Here we focus on the reduction of the benzaldehydes to benzylic alcohols, giving access to nucleophilic substitution chemistry, either to close the bridge with an ether type bridge or to introduce low molecular weight extensions comprising alternative functional groups like e.g. terminal olefins, which would offer ring-closing olefin metathesis (RCM) chemistry as promising bridging chemistry.

In an alternative approach, the bridge might also be closed using suitable bi-functional small molecules, like e.g. a bis-*Wittig* salt or a bis-amine (R in scheme 2). The first one would result in a bis-olefin bridged macrocycle while the second, upon double *Schiff*-base formation would close the bridge with a bis-imine

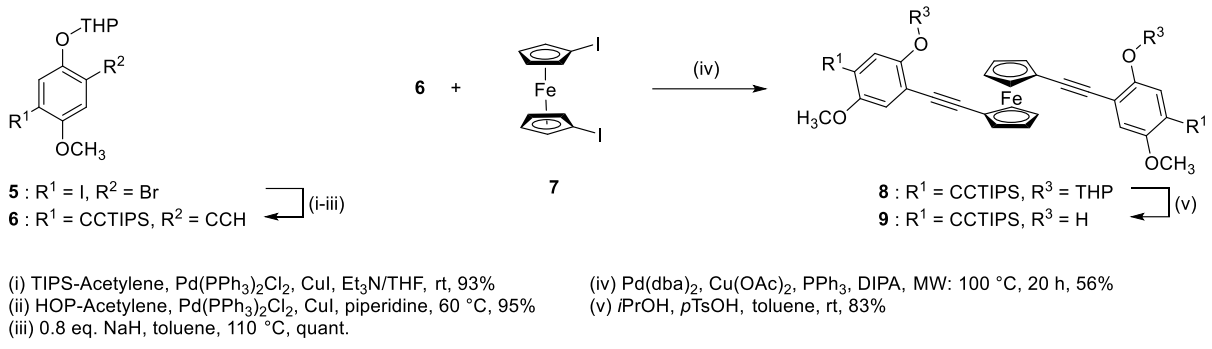
structure. The appealing feature of this strategy would again be its modularity, giving in principle access to structures with various opening angle at the ferrocene joint, as bi-functional small molecules with various spacing between both functional groups could be introduced.



Scheme 2: Different ring closing strategies with the bis-benzaldehyde precursor **4** in common.

Results and Discussion

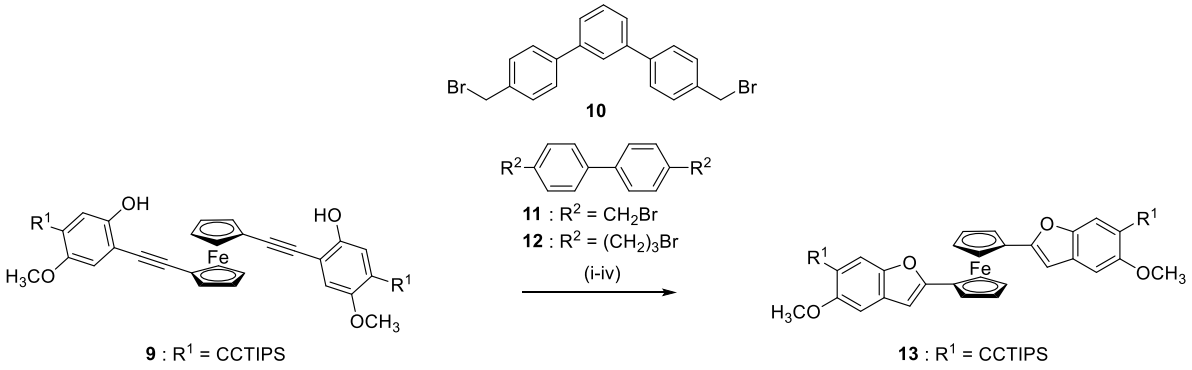
Tempted by the promise of large modularity in the bridging motive, our initial attempts followed the “capping” strategy (scheme 1). And thus the symmetric 1,1’-functionalized ferrocene rod **9** exposing two phenol groups as potential nucleophiles to form bridges with various bis-halides was assembled. The synthesis of **9** is summarized in scheme 3 and comprises the double fold *Sonogashira* cross-coupling of the unsymmetrical acetylene **6** and 1,1’-diiodoferrocene **7** as key step. The required tetrahydropyran protected 2-ethinyl-5-(2’-triisopropylsilylethinyl)-4-methoxyphenol **6** was obtained by adapting an established procedure developed by Höger and coworkers,[10] profiting from the chemoselectivity of iodide compared with bromide in the molecule **5** towards Pd(0) catalyzed cross-coupling conditions.



(i) TIPS-Acetylene, $Pd(PPh_3)_2Cl_2$, CuI, Et_3N/THF, rt, 93%
(ii) HOP-Acetylene, $Pd(PPh_3)_2Cl_2$, CuI, piperidine, 60 °C, 95%
(iii) 0.8 eq. NaH, toluene, 110 °C, quant.
(iv) $Pd(dba)_2$, $Cu(OAc)_2$, PPh_3, DIPA, MW: 100 °C, 20 h, 56%
(v) *i*PrOH, *p*TsOH, toluene, rt, 83%

Scheme 3: Synthesis of the molecular rod **9** comprising a central 1,1'di((*ortho*-phenol)ethynylene)ferrocene subunit.

With the suitably functionalized precursor **9** in hands, numerous attempts to bridge the ferrocene subunit with more or less rigid di-halides were performed unsuccessfully. A representative collection of investigated reaction conditions (i-iv) and di-halides **10**-**12** is displayed in scheme 4. In all investigated nucleophilic reaction conditions the "capping" of the ferrocene junction was not even observed in traces, but the formation of the 1,1'-di(5-methoxy-6-tris(isopropyl)silylethinylbenzofuran-2-yl)ferrocene **13** was detected as main product instead. This product of a double 5-*Endo-Dig* cyclization clearly shows that the deprotonated phenols prefer to undergo an intramolecular nucleophilic attack at the β-carbon of the ethynyl moiety adjacent to the ferrocene in accordance with *Baldwins* rules,[11] compared to the intermolecular reaction with the bridging di-halides. The observed cyclisation of 2-ethynyl substituted phenols to the corresponding benzofuran derivatives has been proposed as versatile synthetic access to the heterobicyclic motive[12] and was already reported by Babin et al before[13].

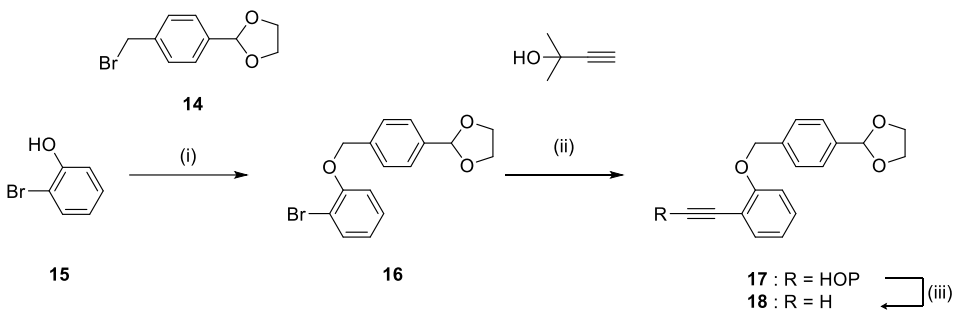


(i) Na_2CO_3, acetone, 70 °C; (ii) NaH, DMF, 80 °C; (iii) NaH, MeCN, 80 °C; (iv) Cs_2CO_3, MeCN, Δ

Scheme 4: Unsuccessful "capping" attempts with the diphenol **9**, which exclusively forms the bis-benzofuran-2-yl ferrocene derivative **13** under basic reaction conditions.

As all attempts to form a macrocyclic structure using the "capping" strategy failed, we refocused our investigation on the "bridge closing" strategy. After all "capping" attempts demonstrated that the phenolate anion in *ortho*-position of the ethynyl group is unacceptable, the "bridge closing" strategy has a twofold

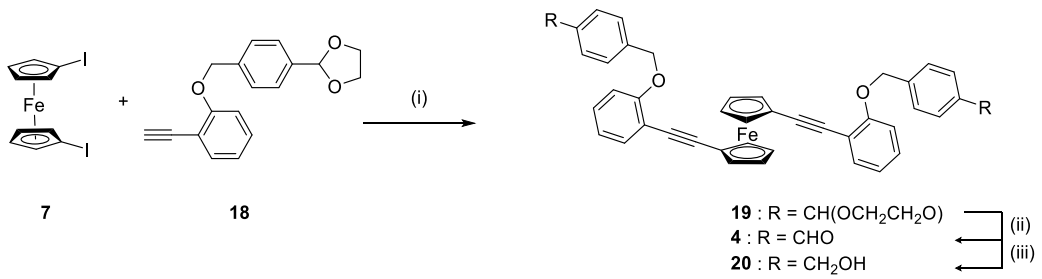
intrinsic beauty. Not only is the phenol masked, but also the masking group itself serves as the building block for the assembly of the bridging structure in a later step. As elaborated in the synthetic strategy above, we aimed for a masking group exposing a benzaldehyde function as promising precursors of a variety of potential macro-cyclization reactions. To avoid interference with the assembly of the precursor **4**, the benzaldehyde group was masked as acetal and introduced as 1,3-dioxolane motif in **14**.



(i) **14**, K_2CO_3, DMF, 80 °C, 94 %; (ii) $Pd(PPh_3)_2Cl_2$, CuI, DIPA/THF, 80°C, 70% ; (iii) NaH, toluene, 110 °C, 70%.

Scheme 5: Synthesis of building block **18**

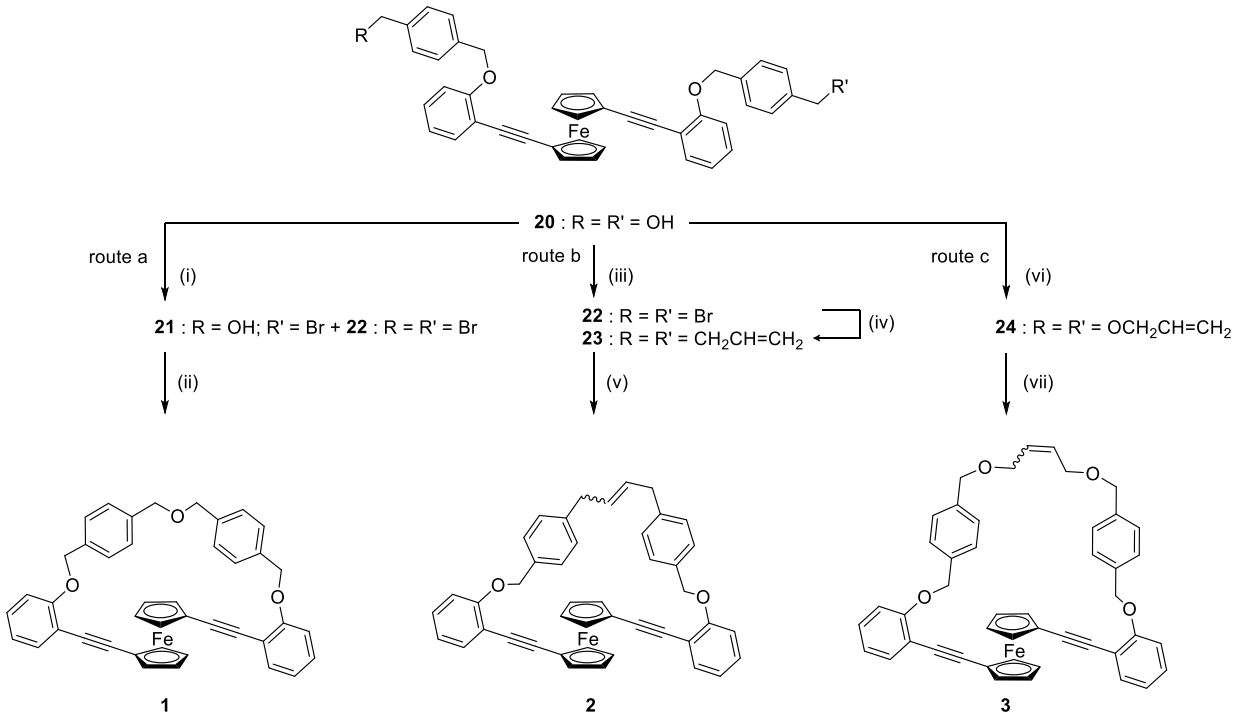
The 2-(4(bromomethyl)phenyl)1,3-dioxolane **14** was prepared within 2 steps according to standard protocols.[14,15] Dioxolane **14** serves as masked aldehyde, compatible with the basic cross coupling conditions shown in Scheme 5. The benzylation of 2-bromophenol **15** was performed under basic conditions using K_2CO_3 in DMF at 80 °C. Palladium-catalyzed *Sonogashira* coupling of aryl bromide **16** with a slight excess of 2-methyl-3-butyn-2-ol was performed in a 1:3 mixture of DIPA/THF, using 6 mol% of $PdCl_2(PPh_3)_2$ and 10 mol% copper(I) iodide. The unprotected aldehyde analogue of **16** was also tested, but afforded the coupling product in low yields only. The use of 2-methyl-3-butyn-2-ol was preferred over silyl protected acetylenes, since the polarity introduced by the propargyl alcohol in **17** enabled easy chromatographic purification.[16] Removal of hydroxypropyl with sodium hydride in refluxing toluene yielded the building block **18** in 72%. Deprotection was also accomplished, yet incomplete, using a 1 M solution of TBAOH in methanol at 75 °C, following Huang's protocol[17].



(i) $Pd(MeCN)_2Cl_2$ (6 mol-%), $P(t\text{-}Bu)_3$ (12 mol-%), CuI, THF/DIPEA, 60 °C, 15 h, 90 %
(ii) PPTS, acetone/water, μW, 80 °C, 10 min, 96 %
(iii) $NaBH_4$, THF, 30 min, 99 %

Scheme 6: Sonogashira cross coupling of FcI_2 and acetylene **18**, subsequent treatment forms dibenzyl alcohol **20**.

Since 1,1'-diethynyleneferrocene readily undergoes cyclization reactions[18], the 1,1'-diiodoferrocene (FcI_2) was selected as ferrocene source. FcI_2 **7** was synthesized in two reaction steps following the protocol of Butler et al.[19] With the compound **18** in hand, we were able to perform the twofold *Sonogashira* coupling reaction shown in Scheme 6. This time however, the reaction conditions developed by Buchwald[20] and coworkers and further optimized for FcI_2 by Inkpen et al.[21] were applied. Thus $Pd(MeCN)_2Cl_2/P(^tBu)_3$ with copper(I) iodide in a DIPA/THF mixture was kept at 60 °C, while a 3:1 ratio of the acetylene **18** was added to FcI_2. The desired symmetrical product **19** was isolated after flash column chromatography (FCC) on silica gel as an orange-red solid in 90% yield. Subsequent cleavage of the acid labile dioxolane **19** was accomplished with pyridinium *p*-toluenesulfonate (PPTS), by transacetalization in an acetone/water mixture.[14,22] The deprotection was performed in a sealed microwave tube and completion was observed after 10 minutes of irradiation at 80 °C. Reduction of the corresponding aldehyde **4** worked in nearly quantitate yields when treated with $NaBH_4$ in THF at room temperature for 30 minutes, forming the Fc derivative **20** exposing two benzylic alcohol groups. Thus, starting from 2-bromophenol and FcI_2, the molecular rod **20** comprising a ferrocene junction and exposing on both sides a benzylic alcohol was available in 6 steps and an over-all yield of 56%.



a) (i) NaH, 2 eq. MsCl, THF, -10°C - rt, 16 h, then 10 eq. LiBr, THF, rt, 2 h, 33% **21**; 40% of **22**; (ii) NaH, 0.5 mM in THF, 2 h, 70% of **1**
b) (iii) NaH, 10 eq. MsCl, THF, -10°C - rt, 16 h, then 20 eq. LiBr, THF, rt, 2 h, 69 % of **22**; (iv) vinylmagnesium bromide, CuI, THF, -78 °C - rt, 15 h, 68 % of **23**; (v) Grubbs Catalyst 1st gen. (7.5 mol-%), 1 mM in DCE, 60 °C, 57 % of **2**
c) (vi) allyl bromide, NaH, THF, 60 °C, 60 % of **24**; (vii) Grubbs Catalyst 1st gen. (7.5 mol-%), 1 mM in DCE, 60°C, 57 % of **3**

Scheme 7: Ring closing reactions to form the proposed dibenzylic bridges in different lengths.

With the bis-benzylic alcohol **20** the three different ring closing strategies displayed in Scheme 7 were investigated. While in the first approach (route a) an intramolecular S_N2-type reaction was considered, the macrocyclizations in the second and third approach were based on a ring closing metathesis reaction of terminal olefins. In the second strategy (route b) olefins were introduced with a Grignard reagent and in the third attempt (route c) terminal olefins were introduced by ether formation. Following the route a (Scheme 7), one of both benzylic alcohols of **20** should be converted in a good leaving group, in order to be attacked intra-molecularly by the other one. Therefore, an oven-dried *Schlenk* flask was purged with argon and charged with a 4.5 mM solution of diol **20** in dry and deoxygenated THF. The reaction flask was cooled to -10 °C and the clear, bright orange solution was treated with sodium hydride under a positive pressure of argon. The mixture was stirred for 20 minutes, before 2.0 equiv. of methanesulfonyl chloride were added via a *Hamilton* syringe. The reaction was allowed to reach room temperature over 16 hours and the progress was monitored by MALDI-ToF MS. Elongated reaction times at room temperature resulted in substantial decomposition of the mesylate intermediates as depicted in Figure S1 (ESI). Gentle heating to 50 °C of the mesylate reaction mixture results in formation of macrocycles in varying ring size as shown in Figure S2 (ESI). Hence, we decided to convert the mesylate intermediates into the bromo analogs by addition of lithium bromide to the reaction mixture.[23] The products **21** and **22** of the statistical reaction showed inherently different polarities on silica gel and were separated from the remaining starting material by flash column chromatography in 33% and 40% respectively. A 0.5 mM suspension of monobromo **21** and excess of sodium hydride in dry THF, gave the desired ether bridged macrocycle **1** in excellent 70% yield after 2 hours at 70 °C (see Figure S3, ESI). Attempts to isolate the reactive mesylate intermediate resulted in extensive loss of compound and formation of poorly soluble, tar-like substance when the crude is concentrated. In contrast the mono- and dibromo derivative **21** and **22** showed considerable stability during workup and characterization. We found this procedure inevitable since alternative *Appel* reactions turned out to be too acidic as several side products arise from the cleavage of the benzyl moiety and subsequent benzofuran formation which we could observe in former attempts. Furthermore, efforts to trigger the ether-bridge formation by activating one benzylic alcohol in an intramolecular *Mitsunobu*-Type reaction failed. The successful macrocyclization was displayed by the mass of the isolated compound recorded by MALDI-ToF-MS (Figure S14 ESI), and further corroborated by ^{1}H-NMR spectroscopy. Naturally, we noticed significant difference in the chemical shifts for the benzylic-CH_2 protons and the ferrocene-CH signals. As depicted in Figure 3, compound **21** nicely shows two separate signals for its methylene protons H^c at 4.63 ppm (s, 2H) (gemimal located to OH) and H^e at 4.44 ppm (s, 2H) (CH_2 next to Br), while in symmetric compound **1** they merge into a common benzyl ether signal H^c at 4.58 ppm (s, 4H) indicated with an arrow. The benzylic protons H^a and H^b in compound **21** are found as two overlapping singlets, and likewise culminate as H^a in macrocycle **1**. More profound, the ferrocene protons of open structure **21** are seen as four pseudo-triplets with α protons H^d at 4.49 ppm (pseudo-t, "*J*" = 1.9 Hz, 2H) and 4.46 ppm (pseudo-t, "*J*" = 1.9 Hz, 2H)) respectively two upfield shifted and overlapping β protons as pseudo-triplets H^f at 4.25 ppm (pseudo-t, "*J*" = 1.9 Hz, 2H) and 4.24 ppm (pseudo-t, "*J*" = 1.9 Hz, 2H)). This splitting can be explained by the magnetic inequivalence of the two α- and respectively, the two β-protons of each Cp ring. Hence the ferrocene protons

of compound **21** are seen as two high-order AA'MM' and BB'XX' spin systems with four signals in total. In contrast, the spectra of fully symmetric macrocycle **1** shows only two pseudo-triplets H^d at 4.61 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) and H^f at 4.30 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) as one AA'MM' high-order spin system.

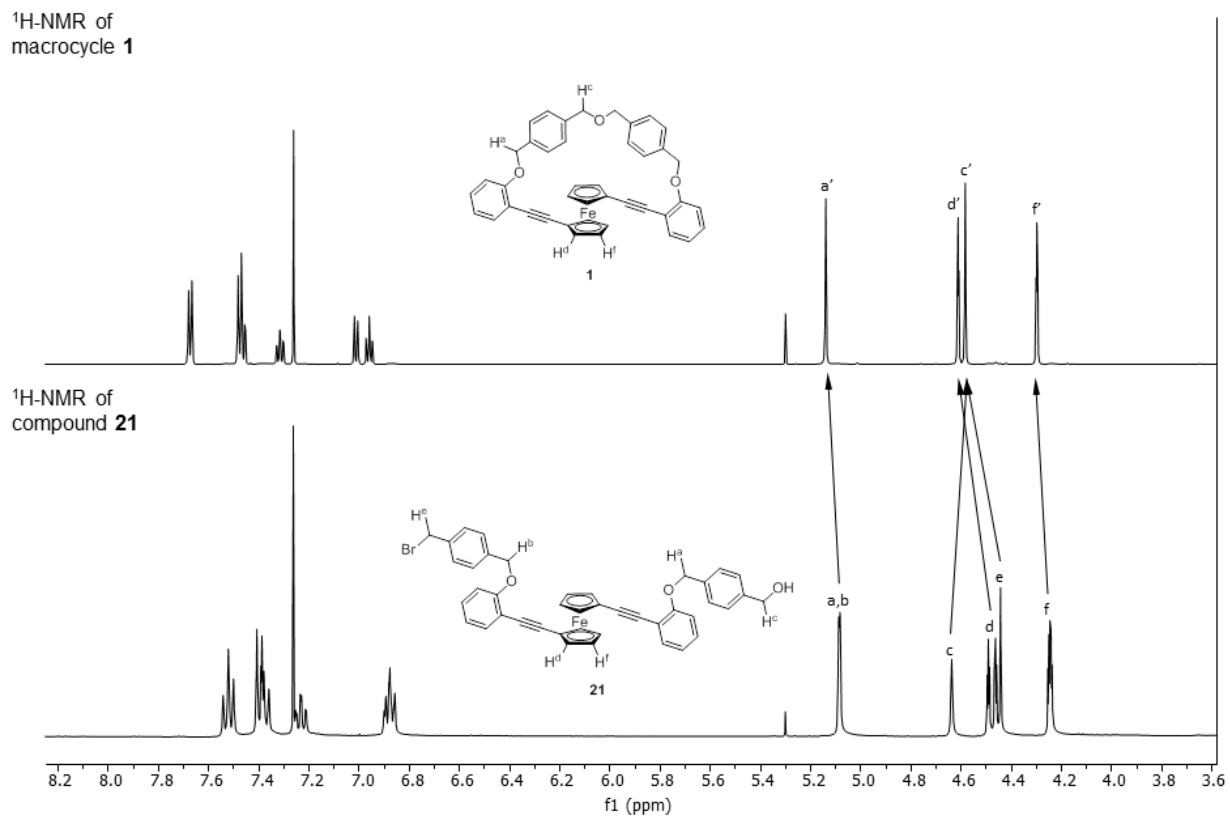


Figure 3: ^{1}H-NMR spectra of compound **1** and **21** in $CDCl_3$ at 20 °C.

In order to obtain a heteroatom free bridging structure we focused on the RCM as potential ring closing reaction (Scheme 7, route b/c). As promising precursor we identified the ferrocene rod **23** exposing two (4-allylbenzyl)oxy substituents. Thus, the diol **20** was converted to the dimesylate derivate (route b Scheme 7), by treatment of the benzylic alcohol with an excess of sodium hydride and subsequent addition of 10 equiv. methanesulfonyl chloride in dry and deoxygenated THF. The reaction was carried out in a Dewar placed Schlenk flask filled with ice and salt, allowing to reach room temperature overnight. Full conversion to the dimesylated adduct was monitored by MALDI-ToF MS after 16 hours (see Figure S3 (ESI). Subsequent addition of 20 equiv. of LiBr in an argon atmosphere reliably gave dibromo derivative **22** after 2 hours at room temperature. The product was isolated in 69% yield after a short column on silica gel, as red oil that crystalized upon standing. Then, dibromo compound **22** was treated with 20 equiv. of a 1 M solution of vinylmagnesium bromide in THF in the presence of 1.0 equiv. copper(I) iodide at -70 °C.[24] Again, the reaction mixture was allowed to warm up to room temperature over 15 h and mass control showed the

full consumption of the starting material. The black reaction mixture was quenched by pouring onto a saturated aqueous solution of NH_4Cl. After extraction the crude was purified by FCC on silica gel and diallylbenzyl **23** was isolated as red/orange oil after 67% yield. Additional side products were eluted by gradually increasing the polarity of the eluent. Interestingly, the mass analysis (MALDI-ToF MS spectra in Figure S4 of the ESI) of these side products pointed at an ethane bridged macrocycle together with di- and trimeric open structures, pointing at intra- and intermolecular *Grignard* reactions of dibromobenzyl **22** under these reaction conditions. With the diolefin in hand, we were able to investigate the RCM reaction. Therefore, a 1.0 mM solution of divinyl **23** in freshly distilled dichloroethane was prepared and heated together with 15 mol-% of *Grubbs* catalyst 1st gen. for 16 hours at 70 °C. Macrocycle **2** was isolated after column chromatography in 57% yield as an inseparable mixture of *E*/*Z* isomers. The formation of an *E*/*Z* mixture was not surprising as we neither used an *E*- or *Z*-selective RCM catalyst, nor our compound bears structural determinants. However, the macrocycle was on the one hand evidenced by mass analysis and on the other hand we identified the configuration of the target compound ***2EZ*** by one- and two-dimensional NMR experiments as depicted in Figure S17 (ESI). Unambiguous determination of the *E* and *Z* isomer is hampered by the symmetry of the two stereoisomeric compounds. The two vinyl protons $H^{aE/Z}$ in ***2EZ*** are symmetry equivalent and isochronous in both cases and the coupling to the two adjacent methylene groups results in magnetically inequivalent protons, that show high-order spectra that cannot be analyzed directly. Consequently, we recorded a 2D-HSQC spectrum that showed a chemical shift difference of 5.3 ppm along the carbon dimension, which allows unambiguous assignment of the major species as the *E* isomer with δ = 38.7 ppm, whereas the minor *Z* isomer resonates at δ = 33.4 ppm (Figure S17 ESI). Figure 4, shows the ^{1}H-NMR spectra of macrocycle **2** and its precursor **23**. Structural transformation is most commanding pronounced by the allyl- and vinyl proton signals. The characteristic vinylic methine proton H^a in **23**, merge from 5.93 ppm (ddt, *J* = 16.9 Hz, 10.2 Hz, 6.7 Hz, 2H) to an overlapping signal for both isomers as $H^{aE/Z}$ at 5.69 ppm (m, 2H). Allylic protons H^f in compound **23** diverge in two for the *E* and *Z* isomer corresponding doublets with H^{fZ} at 3.54 ppm (d, *J* = 5.1 Hz, 2H) and H^{fE} at 3.42 ppm (d, *J* = 4.9 Hz, 2H). The terminal olefin protons H^c in **23** completely disappear in the macrocycle. The structural change affects the benzylic protons H^b slightly, as the change is only Δδ = 0.047 ppm. Finally, the ferrocene signals draw a coherent picture of the formed macrocycle. We recorded H^{dZ} ferrocene protons at 4.63 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) and H^{eZ} at 4.33 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) respectively H^{dE} at 4.61 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) and H^{eE} at 4.29 ppm (pseudo-t, "*J*" = 1.8 Hz, 4H) in accordance with the above stated splitting system for symmetric substituted ferrocenes. The *E*/*Z* ratio was calculated by comparing the integrals for allylic protons H^{fE} and H^{fZ} and was found to be [2.8:1].

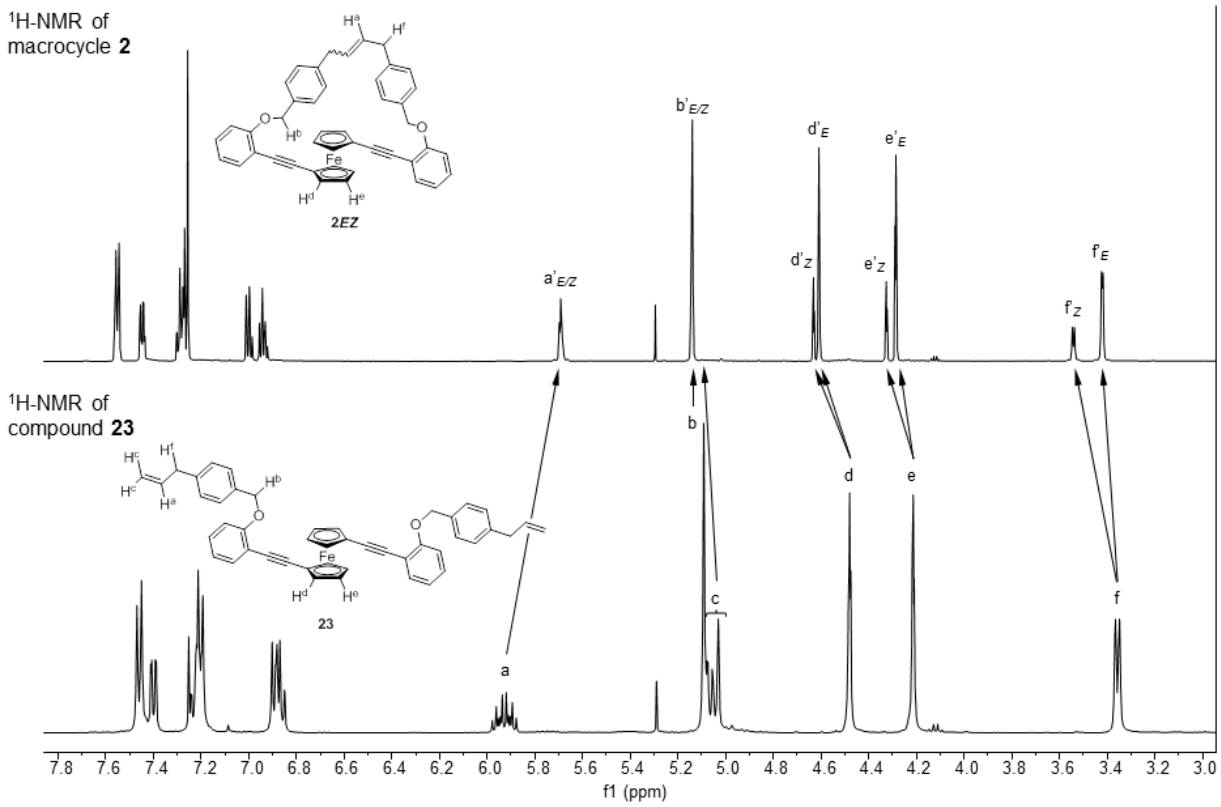


Figure 4: ^{1}H-NMR spectra of compound **2** and **23** in $CDCl_3$ at 20 °C.

To further elongate the bridging unit we planned to connect the benzyl moieties via an allyl ether bridge (route c, Scheme 7). The diol **20** was treated in a dry and deoxygenated THF solution with 4.0 equiv. of sodium hydride at room temperature, followed by the addition of 4.0 equiv. allyl bromide and heating at 60 °C for 5 hours. The product **24** was isolated by column chromatography on silica as an orange solid in 60 % yield. For the final ring closing reaction, diallyl ether **24** was kept at 60 °C in a 1.3 mM solution of dichloroethane and 7.5 mol-% of *Grubbs* catalyst 1st gen. Full conversion was observed after 20 hours and macrocycle **3** was isolated after column chromatography on silica gel in 57% yield as a mixture of *E*/*Z* isomers. The mixture was separated on semi-preparative HPLC to give 73 % of *E* and 27 % of the *Z* isomer. We identified the two isomers by recording a double-quantum filtered, carbon-coupled 1D-HMQC type spectra, where only protons bound to a ^{13}C-nucleus give a detectable signal. The differences in proton-proton coupling constants clearly allow the assignment of the *Z* ($^{3}J_{HH}$= 11.5 Hz) and the *E* isomer ($^{3}J_{HH}$= 15.8 Hz) shown in Figure S19. Further, the ^{13}C-chemical shift difference for the adjacent CH_2-group additionally validates these findings (*E* at 69.9 ppm and *Z* isomer at 65.0 ppm), displaying the well-known gamma-effect.[25] In Figure 5 we pinpoint the structural change with the help of ^{1}H-NMR spectroscopy. Vinylic methine protons H^{a} in **24** at 5.93 ppm (ddt, *J* = 17.2 Hz, 10.4 Hz, 5.6 Hz, 2H) diverges into H^{aE} at 5.88 ppm (m, 2H) in **3*E*** and H^{aZ} at 5.78 ppm (m, 2H) in **3*Z***. The olefin protons H^{b} and H^{c} in compound **24**, disappeared for the *E* and *Z* isomers of the macrocycle **3.** The benzylic protons H^{d} are both shifted slightly

highfield in the macrocycles while methylene protons H^f showed an inverse trend for the *E* and *Z* isomer as H^{fE} at 5.09 ppm (s, 4H) is slightly shifted downfield and H^{fZ} at 4.43 ppm (s, 4H) shifts upfield. More connotatively is the strong downfield shift for the α ferrocene protons going from the open structure in **24** to the closed macrocycle **3*E*** with $\Delta\delta$ = 0.31 ppm for $H^{g'E}$ and $\Delta\delta$ = 0.26 ppm for H^{gZ} in **3*Z***. Less explicit is the change in the β ferrocene protons for **3*E*** with $\Delta\delta$ = 0.22 ppm in H^{hE} and $\Delta\delta$ = 0.22 ppm for H^{hZ} in **3*Z***. We attribute this variation to local magnetic anisotropic effects that arise from "*edge*" pointing aromatic bridging rings that are forced into the ferrocene space. On the other hand, allylic protons H^e in **24** are strongly deshielded, while in the macrocyclic compounds the protons $H^{e'E}$ and $H^{e'Z}$ are twisted out of the olefinic plane and are strongly upfield shifted as depicted in Figure 5.

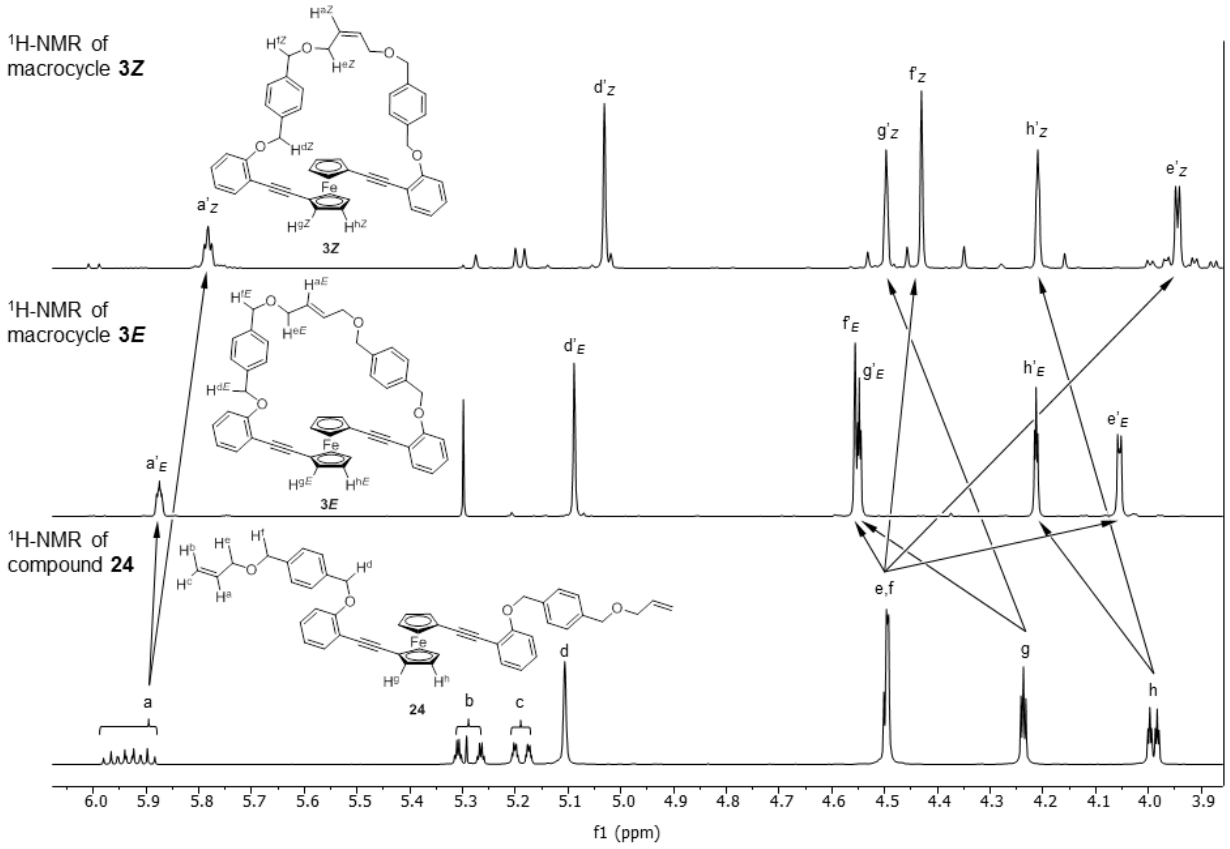


Figure 5: ^{1}H NMR spectra of compound **3*E***, **3*Z*** and **24** in $CDCl_3$ at 20 °C.

Numerous attempts to grow single crystals of the macrocycles **1**-**3** failed, what we initially attributed to a too large flexibility of the bridging structure. This hypothesis was not correct as first single crystals suitable for X-ray diffraction analysis were obtained of the macrocycle **3*Z***, comprising a particular long and flexible bridging structure, by solvent diffusion crystallization in a DCM/2-propanol system. The solid-state structure is displayed in figure 6 and corroborated both, the identity of the compound **3*Z*** and our assignment to the structures based on the NMR spectra. While the structural affirmation is pleasing, the solid-sate structure challenges our molecular design. Obviously, the bridging structure is too flexible to enforce a stretched

arrangement of the phenyl-ethynyl-Fc-ethynyl-phenyl substructure, at least in the solid state. Instead, **3*Z*** crystallizes in a hook shaped arrangement, with nearly parallel-orientated phenylethynyl moieties and a dihedral angle of 9.95° enclosed by both ethynyl groups. The interplanar distance of 3.723 Å measured between both centers of the phenyl rings (d_1 in figure 6), suggests considerable π-π interactions between the OPE subunits. Due to this stacked confirmation, the *Z*-allyl ether bridge forms a loop that is tilted to one side of the macrocycle and causes an O atom distance of only 3.551 Å between O_1 and O_4 (d_2 in figure 6). Another eye-catching structural feature is the proximity of the ferrocene hydrogen atoms and the phenyl rings of the bridiging linker. The ferrocene α and β hydrogen atoms next to the linking loop are both located in the periphery of the phenyl rings, what agrees with the strong low-field proton shift observed for the α and β ferrocene protons upon forming both, the macrocycles **3*Z*** and **3*E*** (Figure 5). The hook shaped arrangement of **3*Z*** is mainly present in the solid-state structure due to crystal packing forces and the dissolved molecule must have a structural flexibility resulting in a single signal for all α and β ferrocene protons respectively, as observed in the ^{1}H-NMR spectrum (Figure 5). Attempts to freeze out the molecular motion were not successful, as the ^{1}H-NMR experiments at -80°C in CD_2Cl_2 still displayed a single signal for all 4 α ferrocene protons. The averaging flexibility of the dissolved molecule must comprise rotational motion around the ferrocene axis as well.

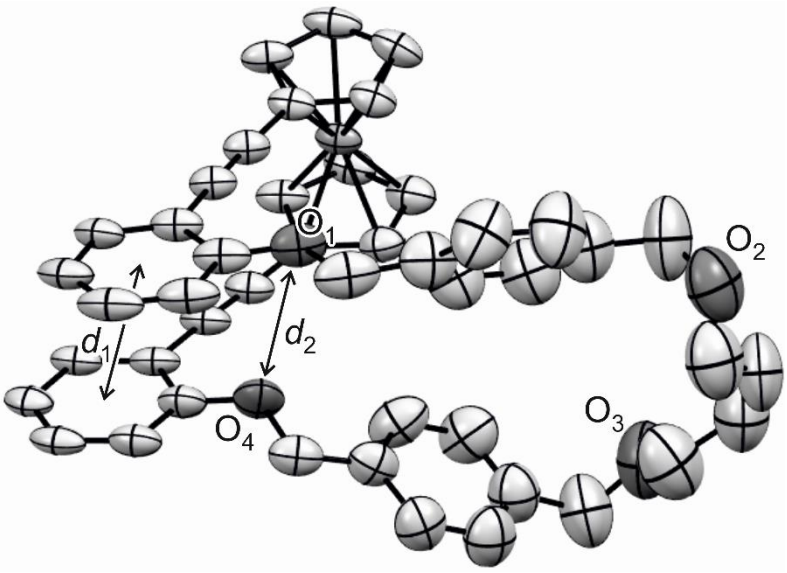


Figure 6: ORTEP plots of the solid-state structure of **3*Z*** with ellipsoids plotted at the 50% probability level.

It is noteworthy that only the macrocycles **3*Z*** and **3*E*** display a pronounced down-field shift of the ferrocene protons, pointing at a to some extent coplanar arrangement of the phenyl rings in the bridging structure and the cyclopentadienyl rings of the ferrocene subunit. For the cyclizations to macrocycles **1**, **2*E*** and **2*Z*** only little effect on the chemical shift of the α and β ferrocene protons was monitored (Figures 3 and 4). This does not exclude a rotation of the ferrocene joint, but implies that the bridge rings are at least less frequently located in plane with the cyclopentadienyl rings in solution.

Conclusion

In the present paper a short and convergent access to rotationally restricted 1,1'-disubstituted ferrocene diphenyethynyls is reported. A "bridge-closing strategy" enabled the formation of the five macrocyclic structures **1**, **2*E***, **2*Z***, **3*E***, and **3*Z*** with various ring sizes, which were obtained either by ring closing metathesis or by an intramolecular nucleophilic substitution reaction. The macrocyclization provided these structures in reasonable yields between 57 and 70% and the mixture of *E*- and *Z*-olefins obtained by the metathesis reaction could only be separated in the case of **3*E*** and **3*Z***. However, the composition of the reaction mixture **2*E*** and **2*Z*** was analyzed by assignment and integration of the NMR peaks.

While the integration of the 1,1'-diphenylene-ethynylene ferrocene subunit in a macrocycle restricts the rotation of the ferrocene axis, the intended fixation of a stretched arrangement of the 1,1'-diphenylene-ethynylene ferrocene junction could not be realized with the presented macrocycles. In contrary, the solid-state structure analysis of **3*Z*** displayed a stacked arrangement of the two OPE subunits. These macrocyclic structures display a dynamic behavior in solution with a large variety of angles between both Fc-interlinked OPE subunits clearly showing that these bridging structures are too flexible to favor a particular arrangement of the Fc junction in solution.

However, the benzaldehyde-functionalized precursor opens a variety of alternative bridge closing reactions and our current focus is set on bridging subunits with increased stiffness.

Experimental Section

General Information: All commercially available compounds were purchased from Sigma–Aldrich, Acros, ApolloScientific, Alfa Aesar, and Fluorochem, and used as purchased. Dry solvents were purchased from Sigma–Aldrich and Acros and stored over molecular sieves (4 Å). $PdCl_2(MeCN)_2$ was synthesized by refluxing $PdCl_2$ in acetonitrile for 1 hr. The resulting solution was filtered through Celite and concentrated to crystallize the product, which was washed with acetonitrile and diethyl ether before drying in air.[21] THF and DCM were distilled from CaH_2 for 6 h in an argon atmosphere. DIPA was distilled and stored over activated 4Å molecular sieve. The reaction flasks used for acetylene deprotection were washed successively with concentrated sulphuric acid, aqu. 1 M NaOH solution and deionized water, then dried under vacuum prior of use. HPLC purification was achieved on a Shimadzu LC-20 AB machine using a Reprosil 100Å Si, 5 µm, 250 x 16 mm column from Dr.Maisch with HPLC grade 2-propanol from Biosolve and hexane form Baker. For column chromatography, usually silica gel P60 (40–63 µm) from Silicycle™ was used and solvents were of technical grade. TLC was performed on silica gel 60 F254 glass plates with a thickness of 0.25 mm purchased from Merck. All 2D Spectra were recorded on a Bruker Ascend 600 MHz Avance III HD equipped with a 5 mm QCI cryogenic probe head. ^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker DPX NMR at 400 and 101 MHz or a Bruker BZH NMR at 250 and 63 MHz. The chemical shifts are reported in parts per million (ppm) relative to tetramethylsilane or a residual solvent peak, and the *J* values are given in

Hz (±0.1 Hz). High-resolution mass spectra (HRMS) were measured as HR-ESI-ToF-MS with a Maxis 4G instrument from Bruker or were recorded with a Bruker solariX spectrometer with a MALDI source. MALDI-TOF mass spectra were recorded with a Bruker Microflex LRF spectrometer and were calibrated by using CsI_3 clusters.[26] DCTB {trans-2-[3-(4-tert-butylphenyl)-2-methyl-2-propenylidene]malononitrile} was used as matrix if needed.[27] GC-MS was performed on a Shimadzu GCMS-2020 SE equipped with a Zebron 5 MS Inferno column which allowed achieving temperatures up to 350 °C. Elemental analyses were measured with an Elementar Vario Micro Cube instrument.

2-(4-(bromomethyl)phenyl)-1,3-dioxolane 14: This compound was synthesized in 2 steps, adapting related protocols.[14,15] An oven-dried two-necked round-bottomed flask was purged with argon and charged with 4-(bromomethyl)benzonitrile (5 g, 24.2 mmol) and dissolved in dry dichloromethane (100 mL). The solution was cooled to -70 °C and then a solution of DIBAL-H (1 M in hexane, 26.7 ml, 26.7 mmol) was added via a dropping funnel. After the addition, the mixture was allowed to warm to 0 °C over a period of 1 h. Then, the mixture was slowly quenched by adding 10 ml of aqueous 1 M HCl solution and then warmed to room temperature. The mixture was eluted with toluene (250 mL) and washed subsequently with aqueous 1 M HCl solution, 1 M NaOH solution, 2 x water and brine. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude product was purified by FCC on silica using EtOAc/c-hexane (1:5) as eluent. Upon evaporation of the solvent, 4-(bromomethyl)benzaldehyde was obtained as an off white solid. **Analytical Data for 14**: Yield: 84% (4220 mg, 21.3 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 10.01 (s, 1H), 7.93 – 7.81 (m, 2H), 7.61 – 7.50 (m, 2H), 4.51 (s, 2H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): δ_C = 191.47, 144.24, 136.14, 130.16, 129.66, 31.94 ppm. MS (EI$^+$, 70eV): *m/z* (%) = 198 (4), 119 (100), 91 (75), 63 (20). EA: C_8H_7BrO (197.97): calcd. C 48.27, H 3.54; found C 48.25, H 3.81.

A round-bottomed flask was charged with 4-(bromomethyl)benzaldehyde (4.1 g, 22.9 mmol), and dissolved in toluene (80 mL). To the solution, ethylene glycol (2.55 ml, 45.7 mmol) and a catalytic amount of p-toluenesulfonic acid (10 mol%) were added and the mixture was refluxed with the aid of a dean stark trap for 12 h. After no more water was segregated, the reaction was stopped and eluted with toluene (100 mL). Then, the mixture was washed with water (2 x 150 mL) and brine. The organic phase was separated, dried over $MgSO_4$, filtered and concentrated under reduced pressure. The product was purified via FCC on silica using EtOAc/c-hexane (1:5) as eluent. Upon evaporation of the solvent, 2-(4-(bromomethyl)phenyl)-1,3-dioxolane (15) was obtained as a colourless liquid which solidifies upon standing. **Analytical Data for 15**: Yield 91 % (5040 mg, 20.8 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.48 – 7.44 (m, 2H), 7.43 – 7.38 (m, 2H), 5.81 (s, 1H), 4.49 (s, 2H), 4.17 – 3.98 (m, 4H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ_C = 138.77, 138.34, 129.16, 126.99, 103.34, 65.41, 33.12 ppm. MS (EI$^+$, 70 eV): *m/z* (%) = 241 (9), 163 (100), 91 (70), 73 (23). EA: $C_{10}H_{11}BrO_2$ (241.99): calcd. C 49.41, H 4.56; found C 49.31, H 4.28, N 0.4.

2-(4-((2-bromophenoxy)methyl)phenyl)-1,3-dioxolane 16: A round-bottomed flask was charged with 2-bromophenol (581 mg, 3.29 mmol) and was dissolved in dry DMF (20 mL). To that solution, 2-(4-

(bromomethyl)phenyl)-1,3-dioxolane (800 mg, 3.29 mmol) and potassium carbonate (919 mg, 6.58 mmol) were added. The mixture was stirred over night at 80 °C. After the reaction was completed, the reaction mixture was poured onto a sat. sol. of aqueous NH_4Cl (100 mL). The aqueous phase was extracted with 3 portions of toluene (50 mL). The organic phases combined and washed with water (2 x 100 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by FCC on silica gel using EtOAc/c-hexane (1:5) as eluent. Upon evaporation of the volatiles the title compound was isolated as an off white solid. **Analytical Data for 16**: Yield 94 % (1050 mg, 3.14 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.56 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.6 Hz, 1H), 7.53 – 7.47 (m, 4H), 6.91 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H), 6.84 (dd, $^3J_{H,H}$ = 7.9 Hz, $^4J_{H,H}$ = 1.4 Hz, 1H), 5.83 (s, 1H), 5.18 (s, 2H), 4.19 – 3.96 (m, 4H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ_C = 155.07, 137.80, 137.75, 133.59, 128.53, 127.11, 126.88, 122.34, 114.04, 112.64, 103.65, 70.61, 65.47 ppm. MS (EI$^+$, 70 eV): *m/z* (%) = 334 (1.5), 163 (67), 119 (15), 91 (100). EA: $C_{16}H_{15}BrO_3$ (335.02): calcd. C 57.33, H 4.51; found C 57.07, H 4.63.

4-(2-((4-(1,3-dioxolan-2-yl)benzyl)oxy)phenyl)-2-methylbut-3-yn-2-ol 17: An oven-dried 25 mL Schlenk tube was purged with argon and charged under the positive pressure of argon with CuI (136 mg, 0.712 mmol, 10 mol%), $Pd(PPh_3)_2Cl_2$ (303 mg, 0.427 mmol, 6 mol%) and aryl bromide (**16**) (2720 mg, 7.12 mmol). The mixture was suspended in a previously deoxygenated mixture of THF and diisopropylamine (15 ml, 3:1). Then, 2-Methyl-3-butyn-2-ol (3.55 ml, 35.6 mmol) was added drop wise via a syringe and the reaction was heated to 80 °C for 15 h. After the reaction was completed, the mixture was suspended on celite, eluting with DCM. The volatiles were removed and the dry powder was subjected to a flash column chromatography on silica gel using EtOAc/cyclohexane (1:3 to 1:1). The solvent was removed under reduced pressure and afforded the title compound as colorless oil. **Analytical Data for 17**: Yield 70% (1650 mg, 4.98 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H = 7.51 – 7.43 (m, 4H), 7.37 (dd, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.7 Hz, 1H), 7.20 (td, $^3J_{H,H}$ = 7.7 Hz, $^4J_{H,H}$ = 1.5 Hz, 1H), 6.88 (d, $^3J_{H,H}$ = 7.5 Hz, 1 H), 6.84 (d, $^3J_{H,H}$ = 8.5 Hz, 1H), 5.79 (s, 1H), 5.09 (s, 2H), 4.14 – 3.94 (m, 4H), 2.83 (s, 1H), 1.60 (s, 6H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ_C = 159.10, 138.10, 137.36, 133.38, 129.59, 126.70, 126.64, 120.91, 112.90, 112.74, 103.51, 98.46, 78.33, 77.21, 69.94, 65.58, 65.28, 31.56, 31.06 ppm. HRMS (ESI-ToF): calcd. for $[C_{21}H_{22}O_4 + Na]^+$ 361.1410; found 361.1418.

2-(4-((2-ethynylphenoxy)methyl)phenyl)-1,3-dioxolane 18: An oven-dried 50 ml round-bottomed flask was equipped with a reflux condenser, purged with argon and charged with hydroxypropyl (**17**) (1171 mg, 3.46 mmol) and dissolved in previously deoxygenated dry toluene (30 mL). Then, NaH (60 % dispersion in mineral oil, 85.2 mg, 2.13 mmol) was added in one portion and the resulting mixture was heated to reflux overnight (12 h). After the reaction was completed, the mixture was eluted with toluene (50 mL) and washed with water (2 x 100 mL) and brine. The organic phase was dried over $MgSO_4$, filtered and the volatiles were removed under reduced pressure. The crude product was purified by column chromatography on silica gel using EtOAc/c-hexane (1:5) as eluent. Upon evaporation of the volatiles the title compound was isolated as

pale yellow oil. **Analytical Data for 18**: Yield 72% (694 mg, 2.48 mmol) ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ_H = 7.52 - 7.46 (m, 5H), 7.28- 7.21 (m, 1H), 6.91 (td, $^{3}J_{H,H}$ = 7.5 Hz, $^{4}J_{H,H}$ = 1.0 Hz, 1H), 6.89 - 6.85 (m, 1H), 5.82 (s, 1H), 5.20 (s, 2H), 4.20 - 3.98 (m, 4H), 3.31 (s, 1H) ppm. ^{13}C-NMR (63 MHz, CDCl3, 25 °C): δ_C = 159.65, 137.92, 137.48, 134.17, 130.11, 126.86, 126.71, 120.82, 112.70, 112.04, 103.54, 81.36, 80.03, 70.09, 65.33 ppm. MS (EI$^+$, 70 eV): *m/z* (%) = 279 (6), 208 (11), 163 (36), 91 (100). EA: $C_{18}H_{16}O_3$ (280.11): calcd. C 77.12, H 5.75; found: C 77.35, H 5.87.

Bis-acetal 19: An oven-dried 15 ml Schlenk tube was purged with argon and charged with $Pd(MeCN)_2Cl_2$ (12.9 mg, 0.049mmol, 6 mol%), copper iodide (15.7 mg, 0.08mmol, 10 mol%) and 1,1´-diiodoferrocene (359 mg, 0.82 mmol) under the positive pressure of argon. Then, freshly distilled and deoxygenated THF (9 mL) together with the ligand P(*t*-Bu)$_3$ (24.8 µL, 0.09 mmol, 12 mol%) was added. Phenylacetylene (**18**) (690 mg, 2.46 mmol) was dissolved in freshly distilled and deoxygenated DIPA (3 ml) and added to the reaction mixture. The oil bath was heated to 60°C and the mixture was stirred overnight (20 h). The black reaction mixture was suspended on celite, eluting with DCM. The volatiles were removed and the dry powder was subjected to a flash column chromatography on silica gel using EtOAc/c-hexane (1:5) as eluent to isolate the mono- and disubstituted **19** ferrocene derivative as red oil. **Analytical Data for 19**: Yield 90% (550 mg, 0.74 mmol).^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.59 - 7.47 (m, 8H), 7.41 - 7.37 (m, 2H), 7.23 - 7.17 (m, 2H), 6.89 - 6.83 (m, 4H), 5.81 (s, 2H), 4.52 (pseudo-t, $^{3}J_{H,H}$ = 1.9 Hz, 4H), 4.26 (pseudo-t, $^{3}J_{H,H}$ = 1.9 Hz, 4H), 4.10 - 3.98 (m, 8H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ_C = 158.98, 138.16, 137.50, 133.16, 128.92, 126.94, 126.60, 120.85, 113.98, 112.65, 103.50, 91.71, 82.63, 72.86, 71.33, 70.00, 67.03, 65.25 ppm. HRMS (MALDI/ESI): calcd. for $[C_{46}H_{38}FeO_6]^+$ 742.2013; found 742.2013.

Bis-aldeyde 4: A 20 mL oven-dried argon flushed microwave vial was charged with bis-acetal **19** (163 mg, 0.219 mmol) and pyridinium p-toluenesulfonate (226 mg, 0.262 mmol) and suspended in a solvent mixture of absolute acetone (12.75 mL) and water (2.25 mL). The microwave vial was sealed and heated in the microwave for 10 min at 80°C. After the vial was cooled to room temperature, the solvent was removed in vacuum and the remaining substance was dissolved in *t*BME (80 mL) and washed with aqueous $NaHCO_3$ (2 x 50 mL), water and brine. The organic phase was dried over $MgSO_4$ and concentrated in vacuum to afford the title compound as a red solid. **Analytical Data for 4**: Yield 87% (125 mg, 0.190 mmol).^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 9.90 (s, 2H), 7.84 (d, $^{3}J_{H,H}$ = 8,1, 4H), 7.67 (d, $^{3}J_{H,H}$ = 7.8 Hz, 4H), 7.38 - 7.34 (m, 2H), 7.22 - 7.16 (m, 2H), 6.88 - 6.82 (m, 2H), 6.78 - 6.73 (m, 2H), 5.01 (s, 4H), 4.57 - 5.50 (m, 4H), 4.36 - 4.31 (m, 4H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ_C = 191.90, 158.52, 144.06, 135.76, 133.07, 129.87, 129.00, 126.98, 121.17, 113.97, 112.32, 91.78, 82.93, 73.00, 70.96, 69.23, 67.50 ppm. HRMS (MALDI/ESI): calcd. for $[C_{42}H_{30}FeO_4]^+$ 654.1489; found 654.1489.

Bis-alcohol 20: An oven-dried, argon flushed 50 mL round-bottomed flask was charged with bis-aldehyde **4** (0.191 mol, 125 mg) and dissolved in dry THF (20 ml). To the clear bright orange solution, $NaBH_4$ (30 mg) was added in one portion. The reaction was stirred for 45 min at room temperature, when TLC showed full

conversion. The reaction mixture was cooled down to 0°C and aq. NH_4Cl (20%, 20 ml) was slowly added. After extraction with *t*BME the combined organic phases were washed with water and brine. After drying over anhydrous $MgSO_4$ the solvent was removed in vacuum. The residue was purified by flash column chromatography on silica gel using EtOAc/cyclohexane (1:1) as eluent to isolate the bis-alcohol **20** as a bright red/orange solid. **Analytical Data for 20**: ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.52 (d, $^3J_{H,H}$ = 7.7 Hz, 3H), 7.39 (dd, $^3J_{H,H}$ = 7.8 Hz, $^4J_{H,H}$ = 1.7 Hz, 2H), 7.35 (d, $^3J_{H,H}$ = 7.9 Hz, 2H), 7.25 – 7.19 (m, 2H), 6.90 - 6.84 (m, 4H), 5.07 (s, 4H), 4.61 (s, 4H), 4.49 (pseudo-t, *J* = 1.9, 4H), 4.24 (pseudo-t, *J* = 1.9, 4H), 1.80 (s, 2H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25 °C): δ_C = 159.21, 140.63, 136.85, 133.28, 129.12, 127.52, 127.30, 120.98, 114.04, 112.64, 100.12, 91.74, 82.85, 72.99, 71.47, 70.21, 65.21 ppm. HRMS (MALDI/ESI): calcd. for $[C_{42}H_{34}FeO_4]^+$ 658.1802; found 658.1802.

Mono-bromomethyl 21: An oven-dried 10 ml round-bottomed flask was flushed with argon and charged with bis-alcohol **20** (15 mg, 22.8 µmol) dissolved in 5 mL freshly distilled and deoxygenated THF. To the mixture, NaH (60% dispersion in mineral oil, 18.2 mg, 456 µmol) was added at -10°C and the resulting suspension was stirred for 20 min, then methanesulfonyl chloride (5.3 µL, 45.6 µmol) was added at -10°C. The reaction mixture was allowed to warm to room temperature overnight. To the reaction mixture, LiBr (39.6 mg, 456 µmol) was added and the reaction was stirred at room temperature for 2 h. After the reaction was finished, the reaction mixture was poured onto water and extracted with EtOAc (2 x 50 ml). The organic phase was washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by flash column chromatography over a silica gel using DCM/cyclohexane, 1:5 to elute the bis-bromo adduct **22** (40%) then EtOAc/cyclohexane, 1:5 was utilized to elute the title compound **21** and EtOAc/cyclohexane, 1:1 to was used to wash out the starting material **20** (21%). The solvent was removed under reduced pressure and afforded the mono-bromomethyl **21** as orange solid. **Analytical Data for 21**: Yield 33% (5.5 mg, 7.28 µmol). ^{1}H NMR (600 MHz, $CDCl_3$, 25°C): δ_H = 7.54 – 7.52 (m, 2H), 7.51 (d, $^3J_{H,H}$ = 8.1 Hz, 2H), 7.41 – 7.38 (m, 4H), 7.37 (d, $^3J_{H,H}$ = 8.0 Hz, 2H), 7.25 – 7.21 (m, 2H), 6.90 – 6.85 (m, 4H), 5.09 (s, 2H), 5.08 (s, 2H), 4.64 (s, 2H), 4.49 (pseudo-t, *J* = 1.9 Hz, 2H), 4.46 (pseudo-t, *J* = 1.8 Hz, 2H), 4.44 (s, 2H), 4.24 (pseudo-dt, *J* = 4.9 Hz, 1.9 Hz, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25°C): δ_C = 159.05, 158.94, 140.49, 137.43, 137.29, 136.47, 133.16, 133.16, 129.19, 128.99, 128.96, 127.40, 127.16, 120.95, 120.83, 113.96, 113.87, 112.58, 112.50, 91.76, 91.60, 82.65, 82.60, 72.87, 72.85, 71.26, 71.23, 70.06, 69.87, 67.12, 67.02, 65.12, 33.27 ppm. HRMS (ESI-ToF): calcd. for $[C_{42}H_{33}BrFeO_3]^+$ 720.0959; found 720.0956.

Ether bridged macrocycle 1: An oven-dried 20 ml round-bottomed microwave vial was flushed with argon, charged with NaH (60% dispersion in mineral oil, 10 mg, 251 umol) and compound **21** (5.5 mg, 7.2 µmol) and dispensed in 15 mL freshly distilled and deoxygenated THF. The suspension was heated to 70°C for 2 h when MALDI mass control indicated complete consumption of the starting material. The reaction mixture was cooled to room temperature, before it was transferred to an Erlenmeyer flask and quenched by dropwise addition of water (50 mL). The organic phase was eluted with ethylacetate and washed with water (2 x 50

mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by column chromatography over a silica gel using with EtOAc/c-hexane (1:3). The solvent was removed under reduced pressure and afforded the ether bridged derivate (**1**) as orange oil. **Analytical Data for 1**: Yield 70% (3.4 mg, 7.62 µmol). ^{1}H NMR (600 MHz, $CDCl_3$, 25°C): δ_H = 7.67 (d, $^3J_{H,H}$ = 7.9 Hz, 4H), 7.50 – 7.44 (m, 6H), 7.35 – 7.28 (m, 2H), 7.01 (dd, $^3J_{H,H}$ = 8.3 Hz, $^4J_{H,H}$ = 1.1 Hz, 2H), 6.96 (td, $^3J_{H,H}$ = 7.5 Hz, $^4J_{H,H}$ = 1.0, 2H), 5.14 (s, 4H), 4.61 (pseudo-t, J = 1.8 Hz, 4H), 4.58 (s, 4H), 4.30 (pseudo-t, J = 1.8 Hz, 4H) ppm. ^{13}C NMR (151 MHz, $CDCl_3$, 25°C): δ_C = 159.22, 137.78, 136.60, 132.65, 129.04, 128.00, 127.21, 120.94, 114.02, 112.19, 92.06, 82.67, 72.52, 72.41, 70.62, 70.03, 65.82 ppm. HRMS (MALDI/ESI): calcd. for $[C_{42}H_{32}FeO_3]^+$ 640.1696; found 640.1696.

Bis-bromomethyl 22: A heat gun dried 5 ml round-bottomed flask was flushed with argon and charged with bis-alcohol **20** (50 mg, 756 umol) dissolved in 5 mL freshly distilled and deoxygenated THF. To the mixture, NaH (60% dispersion in mineral oil, 152 mg, 37 mmol) was added at -10°C and the reaction mixture was stirred for 20 min, then methanesulfonyl chloride (58 uL, 152 umol) was added at -10°C. The reaction was allowed to warm to room temperature overnight. To the reaction mixture, LiBr (133 mg, 1.5 mmol) was added and the reaction was stirred at room temperature for 2 h. After the reaction was finished, the reaction mixture was poured onto water and extracted with EtOAc (2 x 50 ml). The organic phase was washed with water (2 x 50 mL) and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified by filtration over a silica gel plug using with DCM/c-hexane (1:5). The solvent was removed under reduced pressure and afforded the bis-bromomethyl **22** as orange oil that solidified upon standing at 4 °C. **Analytical Data for 22**: Yield 69% (41 mg, 0.052 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.51 (d, $^3J_{H,H}$ = 8.1 Hz, 4H), 7.43 – 7.37 (m, 6H), 7.26 – 7.20 (m, 2H), 6.91 – 6.84 (m, 4H), 5.08 (s, 4H), 4.50 (pseudo-t, J = 1.9 Hz, 4H), 4.45 (s, 4H), 4.27 (pseudo-t, J = 1.9 Hz, 4H) ppm. ^{13}C NMR (101 MHz, $CDCl_3$, 25°C): δ_C = 159.21, 140.63, 136.58, 133.28, 129.12, 127.52, 127.30, 120.98, 114.04, 112.64, 100.12, 91.74, 82.85, 72.99, 71.47, 70.21, 65.21 ppm. HRMS (MALDI/ESI): calcd. for $[C_{42}H_{32}Br_2FeO_2]^+$ 782.0113; found 782.0111.

Bis-allyl 23: A heat gun-dried 5 ml round-bottomed flask was purged with argon and charged with vinylmagnesium bromide (0.7 M solution in THF, 1.5 mL, 1.04 mmol (clear, light brown solution) and CuI (10 mg, 52 umol) and cooled to -78°C. To the stirred suspension, bis-bromomethyl **22** (41 mg, 52 umol) dissolved in freshly distilled and deoxygenated THF (5 ml) was added and the mixture was allowed to reach room temperature overnight. After the reaction was complete, the suspension was poured onto a saturated aqueous NH_4Cl solution (100 mL) and extracted with EtOAc (2 x 50 mL). The combined organic phases were washed with water (2 x 50 mL) and brine (50 mL) then dried over MgSO4, filtered and the volatiles were removed under reduced pressure. The crude was purified by flash column chromatography on silica gel using DCM/cyclohexane (1:10). The solvent was removed under reduced pressure and afforded the bis-allyl **23** as orange oil. **Analytical Data for 23**: Yield 68% (24 mg, 0.035 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.47 (d, $^3J_{H,H}$ = 8.0, 4H), 7.41 (dd, J = 7.5, 1.7, 2H), 7.25 – 7.18 (m, 6H), 6.94 – 6.84 (m, 4H),

5.94 (ddt, $^3J_{H,H}$ = 16.9 Hz, $^3J_{H,H}$ = 10.2 Hz, $^3J_{H,H}$ = 6.7 Hz, 2H), 5.13 – 5.01 (m, 8H), 4.49 (pseudo-t, *J* = 1.9 Hz, 4H), 4.22 (pseudo-t, *J* = 1.9 Hz, 4H), 3.37 (d, $^3J_{H,H}$ = 6.7 Hz, 4H) ppm. ^{13}C-NMR (63 MHz, $CDCl_3$, 25°C): δ_C = 159.21, 139.69, 137.37, 134.82, 133.18, 128.96, 128.73, 127.38, 120.77, 115.84, 113.97, 112.68, 91.68, 82.59, 72.80, 71.42, 70.32, 66.94, 39.94 ppm. HRMS (MALDI/ESI): calcd. for $[C_{46}H_{38}FeO_2]^+$ 678.2217; found 678.2215.

***E/Z*-Butene bridged macrocycle 2:** An oven-dried 50 ml Schlenk flask was purged with Argon and charged with a solution of diene **23** (20 mg, 295 µmol) in freshly distilled dichloroethane (27 mL) and a solution of Grubbs Catalyst, 1st Generation (3.46 mg, 15 mol%) in dichloroethane (3 mL). The reaction mixture was degassed by bubbling argon for 15 min. Then, the flask was closed with a rubber septum and heated to 70°C for 16 h. After the reaction was complete, the mixture was cooled to room temperature and diluted with EtOAc (50 mL). The crude mixture was concentrated and purified by flash column chromatography on silica gel using dichloromethane/cyclohexane (1:10). The solvent was removed under reduced pressure to provide the macrocycle **2** as an orange solid (a mixture of *E/Z*-isomers [73:27]). **Analytical Data for 2**: Yield 57% (11 mg, 0.017 mmol). HSQC resolved ^{1}H,^{13}C spectra is shown in Figure S17 (ESI). ^{1}H NMR (600 MHz, $CDCl_3$, 25°C): δ_H = 7.57 – 7.52 (m, 4H overlapping signals of *E*/*Z*), 7.47 – 7.42 (m, 2H, overlapping signals of *E*/*Z*), 7.32 – 7.25 (m, 4H overlapping signals of *E*/*Z*), 7.02 – 6.97 (m, 2H, overlapping signals of *E*/*Z*), 6.97 – 6.90 (m, 2H, overlapping signals of *E*/*Z*), 5.73 – 5.65 (m, 2H, overlapping signals of *E*/*Z*), 5.16 – 5.13 (m, 4H, overlapping signals of *E*/*Z*), 4.63 (pseudo-t, J = 1.8 Hz, 4H, *Z* isomer), 4.61 (pseudo-t, J = 1.9 Hz, 4H, *E* isomer), 4.33 (pseudo-t, J = 1.8 Hz, 4H, *Z* isomer), 4.29 (pseudo-t, J = 1.8 Hz, 4H, *E* isomer), 3.54 (d, $^3J_{H,H}$ = 5.1 Hz, 4H, *Z* isomer), 3.46 – 3.38 (m, 4H, *E* isomer) ppm. Only proton bound carbons are reported; ^{13}C NMR (151 MHz, $CDCl_3$, 25°C): δ_C = 127.22, 132.72, 128.98, 112.71, 121.00, 130.49, 129.07, 70.20, 72.51, 72.50, 72.51, 72.67, 33.37, 38.70 ppm. HRMS (MALDI/ESI): calcd. for $[C_{44}H_{34}FeO_2]^+$ 650.1904; found 650.1903.

Allyl-ether 24: A 100 ml round-bottomed flask was purged with argon and charged with bis-alcohol **20** (30 mg, 0.045 mmol) and dissolved in freshly distilled THF (50 ml). To the stirred solution, NaH (7.28 mg, 0.18 mmol) was added in one portion at room temperature. After no more gas was produced, allyl bromide (0.016 ml, 0.182 mmol) was added to the mixture and the reaction was heated to 60°C for 5 h. After the reaction was complete, the mixture was quenched with water (50 mL), washed with $NaHCO_3$ (50 mL) and brine (75 mL). The organic layer was dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified via column chromatography over a silica gel using with EtOAc/cyclohexane (1:5). The solvent was removed under reduced pressure and afforded the title compound **24** as an orange solid. **Analytical Data for 24**: Yield 60% (20 mg, 0.027 mmol). ^{1}H NMR (400 MHz, $CDCl_3$, 25°C): δ_H = 7.54 – 7.49 (m, 4H), 7.42 – 7.38 (m, 2H), 7.38 – 7.34 (m, 4H), 7.25 – 7.19 (m, 2H), 6.91 – 6.83 (m, 4H), 5.93 (ddt, $^3J_{H,H}$ = 17.2 Hz, $^3J_{H,H}$ = 10.4 Hz, $^3J_{H,H}$ = 5.6 Hz, 2H), 5.29 (dq, $^3J_{H,H}$ = 17.3 Hz, $^4J_{H,H}$ = 1.7 Hz, 2H), 5.19 (dq, $^3J_{H,H}$ = 10.4 Hz, $^4J_{H,H}$ = 1.3 Hz, 2H), 5.11 (s, 4H), 4.52 – 4.47 (m, 8H), 4.24 (pseudo-t, *J* = 1.9 Hz, 4H), 3.99 (pseudo-dt, *J* = 5.6 Hz, J = 1.4 Hz, 4H) ppm. ^{13}C NMR (63 MHz, $CDCl_3$, 25°C): δ_C = 159.10, 137.91, 136.46,

134.73, 133.18, 128.95, 127.86, 127.16, 120.82, 117.12, 113.97, 112.67, 91.67, 82.65, 72.84, 71.84, 71.34, 71.10, 70.18, 67.04 ppm. HRMS (MALDI/ESI): calcd. for $[C_{48}H_{42}FeO_4]^+$ 738.2428; found 738.2425.

Allyl-ether macrocycle 3: An oven-dried 100 ml Schlenk flask was purged with argon and charged with a solution of allyl ether **24** (29 mg, 393 µmol) in freshly distilled and deoxygenated dichloroethane (29 mL) and a solution of Grubbs Catalyst, 1st Generation (2.4 mg, 7.5 mol%) in dichloroethane (3 mL). The reaction mixture was degassed by bubbling argon for 15 min. Then, the flask was closed with a rubber septum and heated to 70°C overnight. After the reaction was complete, the mixture was cooled to room temperature, concentrated and purified by column chromatography over silica gel using EtOAc/cyclohexane (1:5). The solvent was removed under reduced pressure and afforded the title compound **3** as an orange solid (a mixture of *E/Z*-isomers [73:27]) which were separated by HPLC (silica 100 Å, 2-propanol/hexane [95:5], isocratic elution with 8 mL/min). **Analytical Data for 3**: Yield 57% (16 mg, 0.027 mmol). HSQC and HMQC resolved spectra are shown in Figure S19 (ESI). *E*-isomer of **3**: ^{1}H-NMR (600 MHz, $CDCl_3$, 25°C): δ_H = 7.58 (d, $^3J_{H,H}$ = 7.8 Hz, 4H), 7.44 (dd, $^3J_{H,H}$ = 7.6 Hz, 1.7 Hz, 2H), 7.42 – 7.39 (m, 4H), 7.30 – 7.26 (m, 2H), 6.97 (pseudo-d, $^3J_{H,H}$ = 8.4 Hz, 2H), 6.93 (pseudo-t, $^3J_{H,H}$ = 7.5 Hz, 2H), 5.90 – 5.85 (m, 2H), 5.09 (s, 4H), 4.56 (s, 4H), 4.55 (pseudo-t, *J* = 1.9 Hz, 4H), 4.21 (pseudo-t, *J* = 1.8 Hz, 4H), 4.08 – 4.04 (m, 4H) ppm. Only proton bound carbons are reported; ^{13}C NMR (151 MHz, $CDCl_3$, 25°C): δ_C = 127.29, 132.98, 127.71, 129.05, 112.37, 120.96, 129.53, 69.38, 71.78, 72.47, 69.94 ppm; *Z*-isomer of **3**: ^{1}H NMR (600 MHz, $CDCl_3$, 25°C): δ_H = 7.50 (d, $^3J_{H,H}$ = 7.8 Hz, 4H), 7.37 – 7.33 (m, 2H), 7.29 (d, $^3J_{H,H}$ = 7.8 Hz, 4H), 7.24 – 7.20 (m, 2H), 6.87 (pseudo-d, $^3J_{H,H}$ = 8.3 Hz, 2H), 6.84 (pseudo-t, $^3J_{H,H}$ = 7.5 Hz, 2H), 5.80 – 5.77 (m, 2H), 5.03 (s, 4H), 4.52 – 4.48 (m, 4H), 4.43 (s, 4H), 4.23 – 4.18 (m, 4H), 3.94 (d, $^3J_{H,H}$ = 4.2 Hz, 4H) ppm. Only proton bound carbons are reported; ^{13}C NMR (151 MHz, $CDCl_3$, 25°C): δ_C = 127.32, 133.04, 128.05, 112.50, 120.90, 129.73, 70.17, 72.61, 71.68, 71.21, 65.06 ppm. HRMS (MALDI/ESI): calcd. for $[C_{46}H_{38}FeO_4]^+$ 710.2115, found 710.2113.

Structure Determination by Single-Crystal X-ray Analysis: The intensity data for suitably sized crystals of compound ***3Z*** with the formula $C_{46}H_{38}Fe_1O_4$, M = 710.65 g was collected with a Stoe StadiVari diffractometer at 123K using Ga-K_α radiation with λ = 1.34143 Å. The STOE X-AREA suite has been used for data collection and integration. The structure ***3Z*** was solved by the charge flipping method using the program Superflip to reveal the atomic positions. Least-squares refinement against *F* was carried out on all non-hydrogen atoms using the program CRYSTALS, and Chebychev polynomial weights were used to complete the refinement. Plots were produced using Mercury. The X-ray crystallographic parameters, details of data collection and structure refinement are presented in Tables T1. Crystallographic data (excluding structure factors) for compound ***3Z*** has been deposited with the Cambridge Crystallographic Data Center, the deposition number is CCDC-1453128. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Supporting Information: Supporting figures **S1** – **S4**, Crystallographic data, NMR (^{1}H-, ^{13}C-, HSQC and HMQC), elemental analysis and MS (EI-MS, HR-ESI-MS and HR-ESI-MALDI) spectra.

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Graphic for the table of contents (TOC)

TOC caption: Instead of muscular strength, macrocyclization was applied with the intension to force an OPE-Fc junction in an elongated arrangement.

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