Synthesis and Conformational Analysis of Optically Active Ferrocene Containing Macrocyclic Peptides

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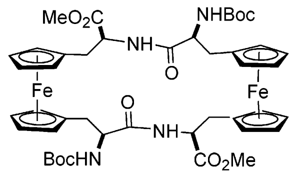
Two macrocyclic peptides **3** and **4** were formed during lactamization of 1,1′-ferrocenylbis(alanine) **1**. Isolation, structure determination, and conformational analysis of **3** and **4** are reported as well as a controlled stepwise synthesis of **4** also including an improved route to **1**. On the basis of their ^{1}H NMR spectra recorded at 300 K in DMSO-d_6, the dimer **3** and trimer **4** were found to be C_2 and C_3 symmetric, respectively. As appeared from computational analysis, the low-energy conformations of the macrocyclic peptides were nonsymmetric. Cyclic voltammetry revealed that the ferrocenyl moieties in **3** or **4** are electrochemically equal to ferrocene.

Introduction

During our work with syntheses of ferrocene-based lactams we observed the formation of byproducts, which were supposed to be oligomers of the parent 1,1′-ferrocenylbis(alanine) derivative **1**.[1] As judged from mass spectroscopic data, the two major compounds were the cyclic dimer **3** and trimer **4**, respectively (Scheme 1).

Since cyclic peptides have received considerable attention due to their biological activities[2−6] we became interested in obtaining **3** and **4** in pure form. A further motivation to this work was the notion that macrocycles containing ferrocene subunits have been synthesized with the goal to be used as redox-active molecular boxes[7] and as ion receptors.[8] A triangular ferrocene-based macrocyclic derivative was very recently described by Dong et al.[9]

Here we report the isolation, structure determination, and conformational analysis of the two major cyclic ferrocenyl peptides **3** and **4** (Figure 1). The structure of cyclotrimer **4** was further confirmed by synthesis, which also included an improved method for **1**. The preferred structural arrangements of **3** and **4** in a vacuum were found by computational analysis, using random Monte Carlo search with Amber* force field and in solution by NMR spectrometric analyses (^{1}H NMR, ^{13}C NMR, COSY, and NOESY). Ferrocene-like electrochemical features were found for **3** and **4** by cyclic voltammetry (CV) studies.



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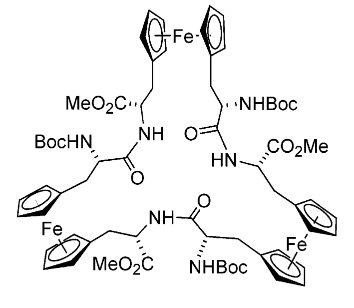

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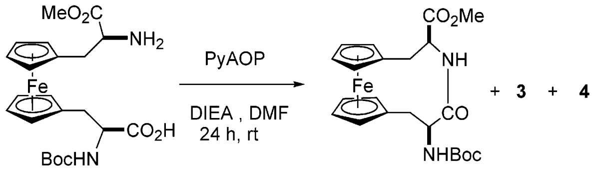
FIGURE 1. Ferrocene-containing macrocyclic peptides **3** and **4**.

SCHEME 1



(S,S)-**1**

(S,S)-**2**

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[5] (a) Wipf, P. *Chem. Rev.* **1995**, *95*, 2115−2134. (b) Michael, J. P.; Pattenden, G. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1−23.

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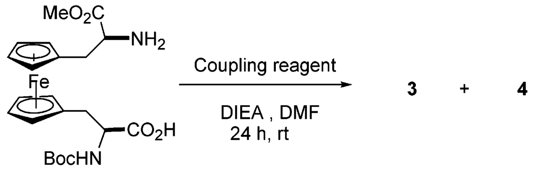
10.1021/jo020353b CCC: $22.00

TABLE 1. Cyclooligomerization of 1,1′-Ferrocenylbis(alanine) Derivative 1



(*S*,*S*)-**1**

reagent[c]	concn of **1** (mM)	yield[a] of **3** + **4** (**3**:**4** ratio[c])
PyAOP	1	27
TFFH	1	0
PyAOP	10	68 (75:25)
HATU	10	56 (72:28)
DPPA	10	44 (77:23)
EDC/HOBt	10	33 (73:27)
PyAOP	21	19[b]

[a] Yields (%) obtained after chromatography. [b] Yield (%) of only cyclic dimer **3**. [c] Determined by normal phase HPLC. [c] List of abbrevations: PyAOP = 7-azabenzotriazol-1-yloxytris(pyrrolidino)phosphonium-hexafluorophosphate, HATU = *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, TFFH = tetramethylfluoroformamidinium hexafluorophosphate, DPPA = diphenylphosphoryl azide, EDC = 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride, HOBt = 1-hydroxybenzotriazole.

Results and Discussions

High dilution lactamization of 1,1′-ferrocenylbis(alanine) derivative **1** with PyAOP as the activation reagent produced a 75% yield of the desired lactam **2** as we previously reported (Scheme 1).[1] In all experiments toward this end we observed various amounts of several side products, two of which were formed in substantial amounts as shown by TLC analysis. Oligomerization was expected and indeed FAB$^+$ mass spectroscopy indicated molecular weights of dimers to pentamers. To maximize the yield of the two major side products we tested some combinations of peptide-coupling reagents and concentrations in the one-pot cyclooligomerization of (*S*,*S*)-**1**. As shown in Table 1, PyAOP as the coupling reagent at 10 mM concentration of (*S*,*S*)-**1** gave the best yield of the isolated cyclodimer/cyclotrimer (75:25) mixture (68–75%). At both higher and lower concentrations markedly lower yields were obtained (19% at 21 mM and 27% at 1 mM). Only dimer **3** could be isolated at higher concentration (21 mM), indicating that dimerization is favored over trimerization. The ratio of **3** and **4** (75:25) did not vary significantly when the reaction was carried out at 10 mM concentration when different coupling reagents were used.

The best separation between the major oligomers **3** (t_R = 10.4 min) and **4** (t_R = 16.7 min) was obtained by normal phase HPLC, using a semipreparative column, and elution under neutral conditions, using a eluent mixture of hexane and *i*-PrOH. Under these conditions 20 mg was the maximum amount of oligomeric mixture that could be separated per injection. The separation resulted in a change of the ratio of **3** and **4** (63:37). Trace amounts of the cyclic tetramer and pentamer were also formed as indicated by FAB$^+$ mass spectroscopy, although these compounds were not isolated (see Supporting Information).

The ^{1}H NMR spectra of **3** and **4** were recorded in $CDCl_3$, which led to broad signals. Especially the NH signals were difficult to detect. as expected, better resolved NMR spectra of these macrocyclic peptides were obtained in DMSO-d_6, which showed that they were similar and were C_2 and C_3 symmetric, respectively. By comparing the ^{1}H NMR (DMSO-d_6) spectra of lactams **2**, **3**, and **4**, it appeared that the main difference was the chemical shifts of the NHBoc- and NHCO-protons. A downfield shift of NHCO-protons was noted as follows—7.55 (**3**), 7.82 (**4**), and 8.44 ppm (**2**)—while an upfield shift of NHBoc-protons was revealed—7.22 (**3**), 6.78 (**4**), and 6.23 ppm (**2**). A large difference in chemical shift of the CHα-protons closest to the NHBoc-group was found for **3** and **4** (3.70 ppm) as compared with that of **2** (4.29 ppm). The multiplicity of the Cp-protons at 4.00–4.20 ppm was different in all three cases and difficult to interpret.

To prepare larger quantities of **4**, as well as obtaining further confirmation of its structure, we embarked on a linear synthesis starting from the fully protected bisamino acid **9**.

We previously reported the synthesis of (*S*,*S*)-**9**,[6,10] but since it required protection/deprotection of 1,1′-diformylferrocene as its monothioacetal using evil smelling and toxic reagents (1,2-ethanedithiol and HgO) we undertook a search for a better route involving acetal formation based on 1,2-diols. As shown in Table 2, four different diols were tested. The monoacetalization with ethylene glycol did not work under the conditions tried (Entry 1 in Table 2), but the substituted glycol derivatives gave the acetals in fair to good yields. In the following Horner–Wadsworth–Emmons (HWE) olefination the acetal **5a** failed to give the desired product, while the other two acetals worked (Entries 3 and 4 in Table 2). Despite a higher yield being obtained in the acetalization to give **5b**, acetal **5c** was chosen for further synthesis since the overall reaction sequence, including the deprotection, gave a higher yield of **7**. Moreover, acetal **5c** was easier to purify than **5b** due to the presence of diastereomers in **5b** and **5c** was also easier to hydrolyze. A second HWE reaction of **7** with the differently protected phosphonate gave the 1,1'-ferrocenylbis(dehydroamino acid) derivative, which was hydrogenated in the presence of [Rh(COD)-((*S*,*S*)-Et-Duphos)]$^+$OTf$^-$ as catalyst to give (*S*,*S*)-**9**.[6]

Hydrogenolysis of (*S*,*S*)-**9** gave **10** having the amino group exposed to form dipeptide **12** (75%) upon EDC/HOBt coupling with **11**,[6] which was obtained from **9** after deprotection with QF (Scheme 2). In the next step, the TMSE group of **12** was removed by QF treatment followed by another peptide coupling with **10** to give the linear tripeptide **13** in 38% yield (over two steps). Next, the TMSE group of **13** was removed to give **14** followed by hydrogenolysis to cleave the Cbz protecting group of **14**, which was then cyclized to **4** by using PyAOP-induced

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(8) (a) Beer, P. D.; Szemes, F. *J. Chem. Soc., Chem. Commun.* **1995**, *21*, 2245–2247. (b) Tendero, M. J. L.; Benito, A.; Lloris, J. M.; Martinez-Manez, R.; Soto, J.; Paya, J.; Edwards, A. J.; Raithby, P. R. *Inorg. Chim. Acta* **1996**, *247*, 139–142. (c) Beer, P. D.; Cheng, Z.; Drew, M. G. B.; Johnson, A. O. M.; Smith, D. K.; Spencer, P. *Inorg. Chim. Acta* **1996**, *246*, 143–150.

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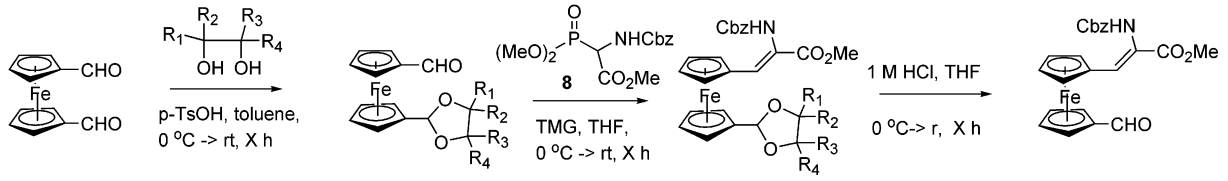
(10) Basu, B.; Chattopadhyay, S. K.; Ritzén, A.; Frejd, T. *Tetrahedron: Asymmetry* **1997**, 1841–1846.

TABLE 2. The Modified Synthetic Path to Compound 7



5a, $R_1 = R_3 = H$, $R_2 = R_4 = Ph$
5b, $R_1 = R_3 = H$, $R_2 = R_4 = Me$
5c, $R_1 = R_2 = R_3 = R_4 = Me$

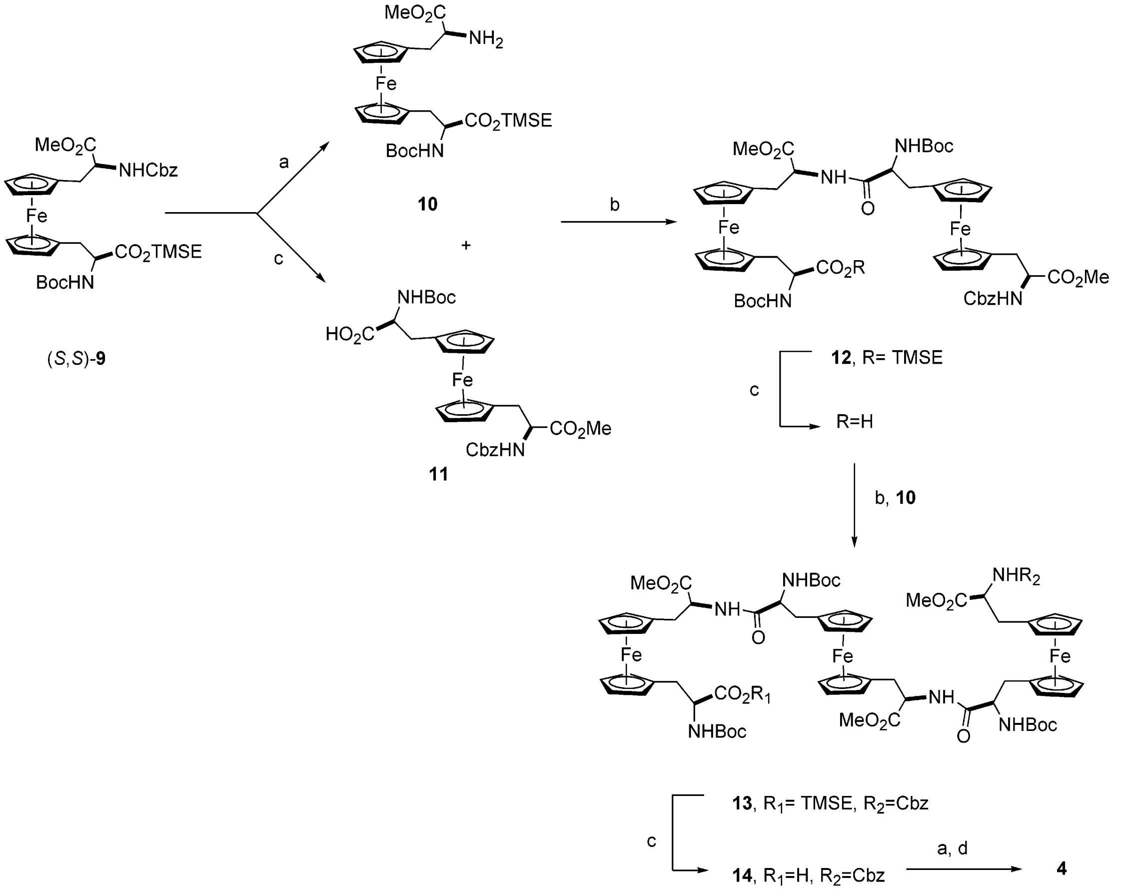
6a, $R_1 = R_3 = H$, $R_2 = R_4 = Ph$
6b, $R_1 = R_3 = H$, $R_2 = R_4 = Me$
6c, $R_1 = R_2 = R_3 = R_4 = Me$

7

					acetalisation		HWE reaction		hydrolysis	
entry	R_1	R_2	R_3	R_4	time (h)	yield[a] (%)	time (h)	yield[a] (%)	time (h)	yield[a] (%)
1	H	H	H	H	24[b]	0				
2	H	Ph	H	Ph	5−6	52	48	0		
3	H	Me	H	Me	3−4	88	48	49	24[c]	49[c]
4	Me	Me	Me	Me	1−2	71	48	67	24	85

[a] The isolated yields. [b] The reaction time was prolonged at higher temperatures but no product was obtained. [c] Formation of several compounds that were difficult to separate.

SCHEME 2[a]



[a] Reagents and conditions: (a) 5% Pd/C, MeOH, H_2 (1 atm), rt, 24 h (89% (**10**), 74% (**14** $R_1 = H$, $R_2 = Cbz$ → **14** $R_1 = R_2 = H$)); (b) EDC, HOBt, DIEA, DMF, rt, 24 h (75% (**12**), 55% (**13**)); (c) TBAF·3H_2O, THF, 0 °C → rt, 24 h (85% (**11**), 44% (**14**), 68% (**12** R = TMSE → **12** R ≃ H)); (d) PyAOP, DIEA, DMF, rt, 24 h (41%).

coupling.[11,12] The resulting cyclic peptide was identical in all respects (optical rotation and ^{1}H NMR, ^{13}C NMR, HRMS, and IR spectra, as well as HPLC retention time) with the material obtained in the direct cyclotrimerization of (*S*,*S*)-**1**.

To determine the low-energy conformations of **3** and **4**, a Monte Carlo based conformational search was made on model compounds **3′** and **4′**, respectively, in which the

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[11] We have noticed that PyAOP was the reagent of choice in cyclization of peptides, which has also been observed by others.[12]

[12] Albericio, F.; Bofill, J. M.; El-Faham, A.; Kates, S. A. *J. Org. Chem.* **1998**, *63*, 9678−9683.

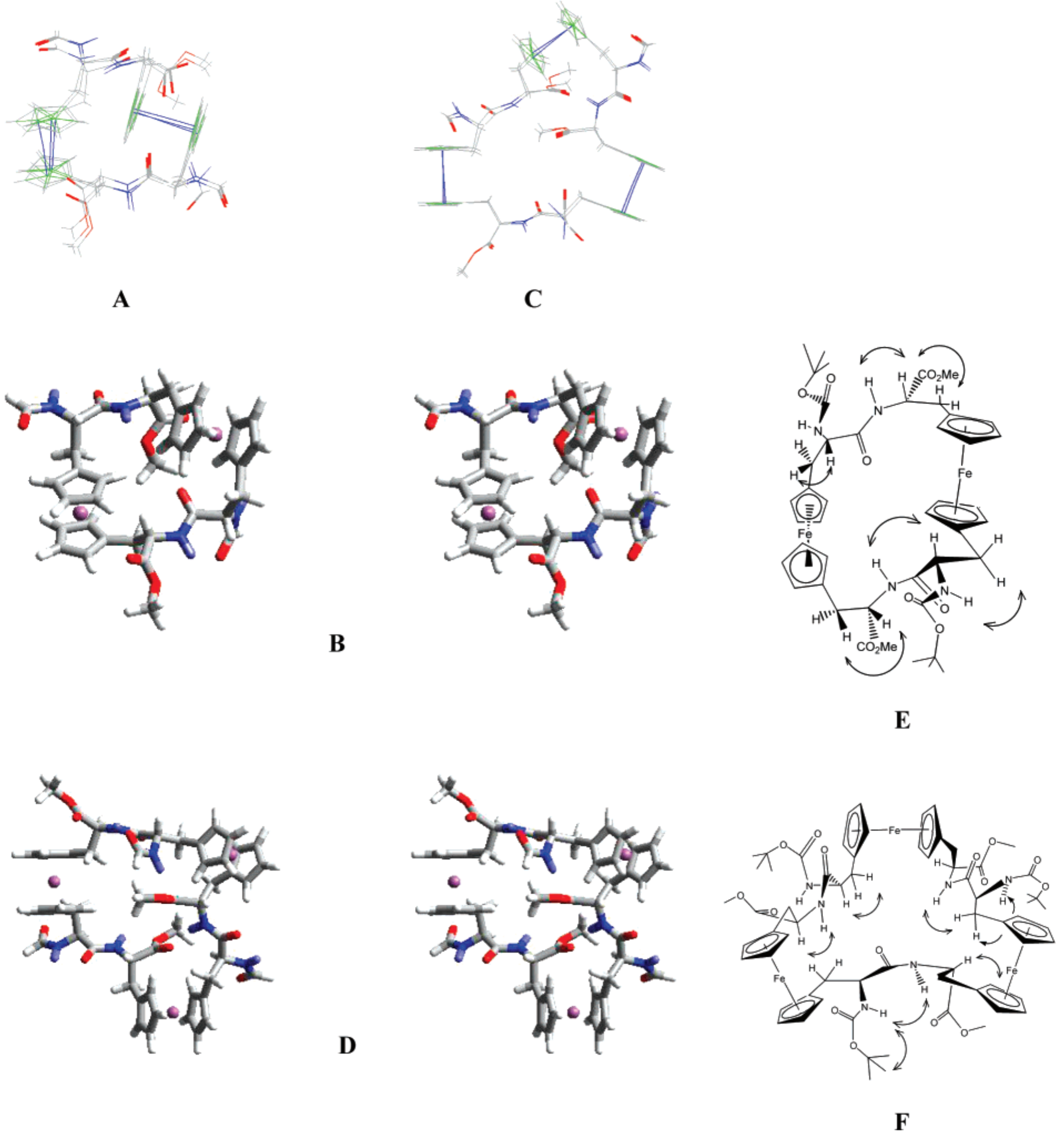

FIGURE 2. The superimposed conformations of dimer **3′** (**A**) and trimer **4′** (**C**) that were found as the low-energy conformations within 3 kcal/mol by conformational search, using Monte Carlo PRCG based minimization and Amber* as a force field. Stereoview of the conformation of dimer (**B**) and trimer (**D**) having the lowest energies found for each of the three conformations of **3′** (**A**) and **4′** (**C**), respectively, by minimization with Monte Carlo TNCG based minimization and the Amber* force field; one of the possible C_n-symmetric ($n = 2$ for **3** and 3 for **4**) conformations of **3** (**E**) and trimer **4** (**F**) based on NOESY and COSY experiments (the strongest NOE:s are shown by arrows) is schematically drawn. List of abbreviations: PRCG = Polak−Ribiere conjugate gradient minimization, TNCG = truncated Newton conjugate gradient, NOESY = nuclear Overhauser effect spectroscopy, COSY = Correlated spectroscopy.

NHBoc groups were replaced by formamide groups (Figure 2). The global minima in a vacuum were obtained for each model compound by using the Macromodel v 7.0 Monte Carlo PRCG based minimization algorithm with random conformational search and Amber* force field.[13] Of 100 Monte Carlo pushes of model compounds **3′** and **4′**, 8 and 9 unique conformations were found, respectively. For each of compounds **3′** and **4′**, three and two low-energy conformations were found within 3 kcal/mol, respectively. The energetically lowest conformation of **3′** was 1.9 kcal/mol lower than the second, which was 0.3 kcal/mol lower than the third conformation (Figure 2A). For trimer **4′**, the energetically lowest conformation was 2.6 kcal/mol lower than the second conformation (Figure 2C). When the energetically lowest conformations were

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(13) Mohamadi, F.; Richards; N. G. J.; Guida, W. C.; Liskamp, R.; Lipton, M.; Caufield, C.; Chang, G.; Hendrickson, T.; Still, W. C. Macromodel V7.0. In *J. Comput. Chem.* **1990**, *11*, 440−467.

compared with the other conformations, the only significant difference was found in the spatial orientation of the CO_2Me group.

Thereafter the lowest energy conformations of model compounds **3′** and **4′** (shown in Figure 2, parts A and C, respectively) were fully energy minimized separately by the Monte Carlo TNCG based minimization algorithmic method and Amber* force field.[13] As a result, the conformations shown in panels B and D of Figure 2 were obtained for **3′** and **4′**, respectively.

The signals in the ^1H NMR spectra could be assigned by COSY experiments, and based on NOESY couplings (Supporting Information) the conformations of **3** and **4** could be drawn schematically (Figure 2, parts E and F, respectively). A significant difference was found between the conformations obtained from NOESY couplings in DMSO-d_6 (polar solvent) and from Monte Carlo minimization in a vacuum, as shown in Figure 2. In solution the C_2- and C_3-symmetric conformations were observed, which was not supported by the conformations obtained by the computations. This is most likely due to the different environments in the two cases.

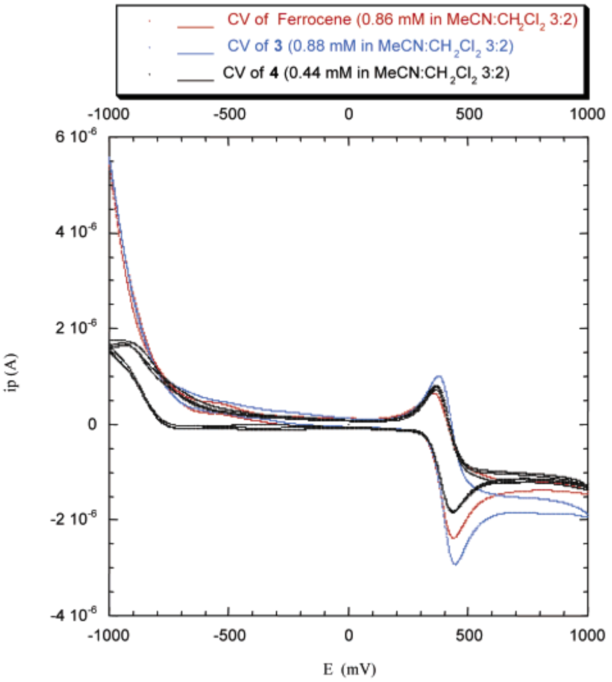
To gain information about the redox features of **3** and **4**, their cyclic voltammograms were recorded (MeCN:CH_2Cl_2 3:2, Pt anode, TBAP, 25 °C). A single reversible redox wave was observed in both cases ($E_{1/2}(\mathbf{3}) = 413$ mV and $E_{1/2}(\mathbf{4}) = 402$ mV vs double junction electrode, $\Delta E(\mathbf{3}) = 68$ mV and $\Delta E(\mathbf{4}) = 68$ mV, at 0.2 v/s scan rate), indicating that the ferrocene units in **3** and **4** were electrochemically equivalent (Figure 3). Fast rotational change and/or symmetric conformation of **3** and **4**, allowing all ferrocene units a synchronized approach to the electrode surface within the electrochemical time scale, could explain the electrochemical equivalency of ferrocene units. A similar rotational behavior was observed for ferrocene-containing dendrimers.[14] The appearance of a small stripping cathodic peak was observed, when comparing the peaks of the redox wave of **3** and ferrocene, respectively, which indicated a solubility change of the compounds after oxidation. In summary, we observed a negligible change in redox potential going from ferrocene to **3** or **4**, which indicated that there is no electronic communication between the redox centers in these compounds.

Conclusion

Dimer **3** and trimer **4** were obtained from one-pot cyclooligomerization of **1** in a 75:25 ratio and were separated by normal phase semipreparative HPLC. The precursor **1** was obtained via an improved synthetic path. Computational analysis, using random Monte Carlo search and Amber* force field in a vacuum, indicated that **3** and **4** favored nonsymmetric conformations. NMR spectroscopy (DMSO-d_6) indicated C_2 symmetry for **3** and C_3 symmetry for **4**. Cyclic voltammetry showed that all ferrocene units behaved as ferrocene itself and show equal access to the electrode surface.

Experimental Section

General. TLC analyses were preformed on Merck Silica Gel 60 coated glass plates. For column chromatography Meterx (35−70 μm) silica gel was used. ^1H NMR and ^{13}C NMR spectra were recorded on a 400- or 500-MHz spectrometer at 300 K.



Compound	$E_{1/2}$ (ox)[a]	ΔE[b]	| ipa/ipc |
Ferrocene	400	81	0.61
3	413	68	0.69
4	402	68	0.95

[a] $E_{1/2}$ (ox) = (Epa+Epc)/2; [b] ΔE = \| Epa-Epc \|

FIGURE 3. Cyclic voltammogram of ferrocene, **3**, and **4** (MeCN:CH_2Cl_2 3:2, Pt anode, 0.1 M TBAP, 25 °C) at 0.2 v/s scan rate and corresponding electrochemical data.

[α] (=$[\alpha]_D$) values are given in units of 10^{-1} deg cm^2 g^{-1} and concentrations are given in g/100 mL. The following starting materials were prepared according to literature procedures: **8**,[15] 1,1′-diformylferrocene,[16] **9**,[6,10] **11**,[6] and $[Rh(COD)((S,S)\text{-Et-Duphos)}]^+OTf^-$.[17] Unless otherwise noted, reactions were carried out under a dry N_2 atmosphere. Electrochemical measurements were taken on a BAS model 100 A potentiostat. A platinum wire working electrode, a platinum disk auxiliary electrode (of area 0.4 cm^2), and a double junction reference electrode were used in a three-electrode configuration. All electrochemical experiments were carried out under a helium atmosphere at 25 °C, using 0.44, 0.88, and 0.86 mM sample concentrations of **3**, **4**, and ferrocene, respectively, in MeCN:CH_2Cl_2 3:2 with tetrabutylammonium perchlorate (TBAP, 0.1 M) as a supporting electrolyte.

General Procedure for Cyclooligomerization Procedure of (*S*,*S*)-1. Diisopropylethylamine (2.2 equiv) and PyAOP (1.1 equiv) were added to a *X* mM (see Table 1) solution of

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[14] (a) Sengupta, S.; Sadhukhan, S. K. *Organometallics* **2001**, *20*, 1889−1891. (b) Alvarez, J.; Ren, T.; Kaifer, A. E. *Organometallics* **2001**, *20*, 3543−3549. (c) Tárraga, A.; Molina, P.; Curiel, D.; Velasco, M. D. *Organometallics* **2001**, *20*, 2145−2152.

[15] Schmidt, U.; Lieberknecht, A.; Wild, J. *Synthesis* **1984**, 53−60.

[16] Mueller-Westerhoff, U. T.; Yang, Z.; Ingram, G. *J. Organomet. Chem.* **1993**, *463*, 163−167.

[17] Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.

1,1'-ferrocenylbis(alanine) derivative **1** in DMF (10 mL) at room temperature. The resulting solution was stirred at room temperature for 24 h and then the solvent was removed under reduced pressure. The residue was dissolved in EtOAc and worked up as follows: washing of the organic phase with water and brine, followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The crude product was column chromatographed (SiO_2, $CHCl_3$:MeOH:AcOH 120:2:0.5) to give a mixture of cyclic peptide products (yield see Table 1) as yellow oils. Then the cyclic peptides **3** and **4** were separated by HPLC with use of a semipreparative normal phase column (YMC-pack SIL, 300 × 4.6 mm) with isocratic elution (eluent: hexane:isopropanol 92:8, flow rate 1 mL/min) during 30 min. The peaks at $t_R = 10.4$ and 16.7 min were found to be **3** and **4**, respectively (see Supporting Information).

(2*S*,5*S*,8*S*,11*S*)-2,8-[Methoxycarbonyl]-3,9-aza-3,10-oxo-5,11-[(*tert*-butoxycarbonyl)amino]-[6.6](1,1′)ferrocenophane (3): $[\alpha]^{20}$ +11° (*c* 0.18, MeOH); IR (neat) $\bar{\nu}_{max}$ 3321.2, 2931.6, 1747.4−1651.0 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.27 (s, 18H), 2.61−2.81 (m, 8H), 3.55 (s, 6H), 3.70 (t, $J = 8.3$ Hz, 2H), 3.86−4.16 (m, 19H), 4.38 (br s, 2H), 7.21 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 7.2$ Hz, 2H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 28.5, 52.3, 53.7, 58.4, 67.8, 68.4, 68.6, 69.8, 70.2, 70.8, 71.8, 78.7, 82.7, 84.7, 155.5, 171.4, 171.6; HRMS (FAB$^+$) *m*/*z* calcd for $C_{44}H_{56}Fe_2N_4O_{10}$ 912.2695, found 912.2712. Anal. Calcd for $C_{44}H_{56}Fe_2N_4O_{10}$: C, 57.91; H, 6.18; Fe, 12.24; N, 6.14; O, 17.53. Found: C, 58.11; H, 6.15; Fe, 12.34; N, 6.22.

(2*S*,5*S*,8*S*,11*S*,14*S*,17*S*)-2,8,14-[Methoxycarbonyl]-3,9,-15-aza-4,10,16-oxo-5,11,17-[(*tert*-butylcarbonyl)amino]-[6.6.6](1,1′)ferrocenophane (4): $[\alpha]^{20}$ +9° (*c* 0.14, $CHCl_3$); IR (neat) $\bar{\nu}_{max}$ 3330, 2986, 1740−1650 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6) δ 1.32 (s, 27H), 2.67−2.81 (m, 12H), 3.62 (s, 12H), 3.80 (br s, 6H), 4.02−4.11 (m, 24H), 4.26 (br s, 6H), 6.75 (m, 6H), 7.8 (m, 6H); ^{13}C NMR (400 MHz, DMSO-d_6) δ 29.1, 52.7, 54.8, 68.73, 68.9, 69.1, 70.0, 70.1, 71.1, 71.8, 79.7, 84.3, 85.3, 155.9, 172.3, 172.6; HRMS (FAB$^+$) *m*/*z* calcd for $C_{66}H_{84}Fe_3N_6O_{15}$ 1368.4043, found 1368.4033. Anal. Calcd for $C_{66}H_{84}Fe_3N_6O_{15}$: C, 57.91; H, 6.18; Fe, 12.24; N, 6.14; O, 17.53. Found: C, 57.68; H, 6.12; Fe, 12.14; N, 6.08.

General Procedure for Acetalization of 1,1′-Diformylferrocene. *p*-Toluenesulfonic acid (0.34 g, 1.79 mmol) and alkyldiol (0.87 mmol) were added to a mixture of 1,1′-diformylferrocene[16] (0.21 g, 0.87 mmol) in toluene (32 mL) at 0 °C. The resulting solution was stirred at room temperature for *X* h (see Table 2) and then worked up as follows: washing of the reaction mixture with aqueous saturated $NaHCO_3$ followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue was column chromatographed (SiO_2, heptane:EtOAc 1:1) to give **5a−c** (yield see Table 2) as red oils.

1-[2-((4*S*,5*S*)-4,5-Diphenyl-1,3-oxolanyl)]-1'-formylferrocene (5a): IR (neat) $\bar{\nu}_{max}$ 3031.9, 2877.6, 1681.8, 1095.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.38 (s, 2H), 4.60−4.92 (m, 8H), 6.25 (s, 1H), 7.27−7.41 (m, 10H), 10.02 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 69.0, 69.2, 70.5, 70.6, 71.0, 74.5, 85.7, 86.9, 87.5, 103.2, 126.9, 127.2, 128.7, 129.0, 129.1, 136.9, 138.3, 194.4; HRMS (FAB$^+$) *m*/*z* calcd for $C_{26}H_{22}FeO_3$ 438.0918, found 438.0919.

1-[2-(4,5-Dimethyl-1,3-oxolanyl)]-1'-formylferrocene (5b): IR (neat) $\bar{\nu}_{max}$ 2977.9, 1681.8, 1095.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17−1.38 (m, 6H), 3.65−3.73 (m, 2H), 4.20−4.88 (m, 8H), 5.75 (s, 1H), 9.99 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.3, 17.4, 68.8, 68.9, 69.1, 70.3, 70.4, 79.8, 70.9, 71.3, 74.3, 74.6, 78.9, 80.6, 100.9, 194.4; HRMS (FAB$^+$) *m*/*z* calcd for $C_{16}H_{18}FeO_3$ 314.0605, found 314.0609.

1-[2-(4,4,5,5-Tetramethyl-1,3-oxolanyl)]-1′-formylferrocene (5c): IR (neat) $\bar{\nu}_{max}$ 2977.9, 1681.8, 1087.8−1038.85 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 6H), 1.24 (s, 6H), 4.24 (t, $J = 1.9$ Hz, 1H), 4.41 (t, $J = 1.9$ Hz, 1H), 4.60 (t, $J = 1.9$ Hz, 1H), 4.79 (t, $J = 1.9$ Hz, 1H), 5.75 (s, 1H), 9.94 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.5, 24.6, 69.1, 70.3, 70.8, 74.0, 82.9, 88.5, 98.5, 194.4; HRMS (FAB$^+$) *m*/*z* calcd for $C_{18}H_{22}FeO_3$ 342.0918, found 342.0920.

General Procedure for the HWE Olefination Reaction of 5a−c. A solution of **5a−c** (0.268 mmol) in THF (1.2 mL) was added to a mixture of **8**[15] (0.11 g, 0.32 mmol) and TMG (37 μL, 0.30 mmol) in THF (1.2 mL) at 0 °C. The resulting solution was stirred at room temperature for *X* h (see Table 2) and then diluted with EtOAc and worked up as follows: washing of the reaction mixture sequentially with water and aqueous saturated $NaHCO_3$ followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue was column chromatographed (SiO_2, heptane:EtOAc 1:1) to give **6a−c** (yield see Table 2) as red oils.

(*Z*)-1-{2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-1′-[2-(4,5-dimethyl-1,3-oxolanyl)]ferrocene (6b): IR (neat) $\bar{\nu}_{max}$ 3294.2, 1716.5 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16−1.31 (m, 6H), 3.68−3.79 (m, 4H), 4.19−4.20 (d, $J = 6.27$, 4H), 4.43 (s, 2H), 4.43−4.63 (m, 2H), 5.18 (s, 2H), 5.84 (s, 1H), 7.13 (br s, 1H), 7.23 (br s, 1H), 7.34 (br s, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.0, 17.2, 52.6, 67.5, 68.7, 69.3, 69.8, 71.5, 71.8, 71.9, 75.0, 75.7, 79.0, 80.7, 86.6, 101.4, 122.6, 128.5, 128.7, 128.9, 128.9, 134.2, 135.5, 136.9, 155.3, 165.8; HRMS (FAB$^+$) *m*/*z* calcd for $C_{27}H_{29}FeO_6$ 519.1344, found 519.1339.

(*Z*)-1-{2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-1′-[2-(4,4,5,5-tetramethyl-1,3-oxolanyl)]-ferrocene (6c): IR (neat) $\bar{\nu}_{max}$ 3294.2, 1720.4 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21−1.27 (m, 12H), 3.75 (br s, 3H), 4.19 (s, 4H), 4.42 (s, 2H), 4.63 (s, 2H), 5.18 (s, 2H), 5.85 (s, 1H), 7.23−7.26 (d, $J = 10.4$, 1H), 7.34 (br s, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 22.2, 24.3, 52.5, 69.6, 71.7, 76.9, 83.5, 87.4, 99.1, 122.68, 128.4, 128.8, 128.9, 136.0, 137.0, 155.2, 166.2; HRMS (FAB$^+$) *m*/*z* calcd for $C_{29}H_{33}FeO_6$ 547.1657, found 547.1671.

(*Z*)-1-{2-[(Benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethenyl}-1′-formylferrocene (7). A 1 M solution of HCl in water (1.2 mL) was added to a mixture of **6c** (3.50 g, 6.40 mmol) in THF (250 mL) at 0 °C. The resulting solution was stirred at room temperature for 24 h and then diluted with EtOAc (400 mL) and worked up as follows: washing of the reaction mixture sequentially with 1 M NaOH (aq), followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue (4.34 g) was column chromatographed (SiO_2, heptan:EtOAc 1:1) to give **7** (2.43 g, 85%) as a red oil: IR (neat) $\bar{\nu}_{max}$ 3128.6, 1714.6 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 4.45−4.75 (m, 8H), 5.19 (s, 2H), 7.21 (s, 1H), 7.38 (br s, 5H), 9.88 (s, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 52.9, 67.9, 71.5, 72.3, 72.5, 75.0, 78.5, 80.5, 128.7, 127.0, 134.1, 165.8, 193.9; HRMS (FAB$^+$) *m*/*z* calcd for $C_{23}H_{21}FeO_5$ 447.0769, found 447.0757.

(*S*,*S*)-1-[2-Amino-2-(methoxycarbonyl)ethyl]-1′-{[2-(*tert*-butoxycarbonyl)amino]-2-[(2-trimethylsilyl)-ethoxycarbonyl]ethyl}ferrocene (10). Pd/C (5%, 119 mg) was carefully added (Warning! Fire hazard) to a solution of **9** (397 mg, 0.56 mmol) in methanol (50 mL). The mixture was stirred under 1 atm of H_2(g) for 24 h at room temperature. The catalyst was then removed by filtration through Celite and the filtrate was concentrated to give product **10** (276 mg, 89%) as a yellow syrup: $[\alpha]^{21}$ +42 (*c* 0.35, $CHCl_3$); IR (neat) $\bar{\nu}_{max}$ 3400, 2960, 1720 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.09 (s, 9H), 0.95 (t, $J = 8.4$ Hz, 2H), 1.39 (s, 9H), 2.62−2.80 (m, 4H), 3.47 (t, $J = 4$ Hz, 1H), 3.63 (s, 3H), 3.89−4.02 (m, 8H), 4.11 (t, $J = 6$ Hz, 2H), 4.33 (br s, $J = 6.7$ Hz, 1H); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.1, 17.8, 28.7, 35.7, 52.3, 55.0, 56.2, 64.0, 69.2, 69.3, 70.0, 70.1, 70.2, 82.8, 83.9, 155.4, 172.3, 174.8; HRMS (FAB$^+$) *m*/*z* calcd for $C_{27}H_{42}FeN_2O_6Si$ 574.2162, found 574.2170.

1-{{(*S*)-2-{(*S*)-2-{(*S*)-1′-[[2-(*tert*-Butoxycarbonyl)amino]-2-[((2-trimethylsilyl)ethoxycarbonyl)ethyl]]ferrocenyl}-(methoxycarbonyl)ethyl}aminoacyl}-2-(*tert*-butoxycarbonyl)aminoethyl}-(*S*)-1′-[[2-(benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]ferrocene (12). A solution of **10**

(193 mg, 0.34 mmol) in DMF (2 mL) was added to a mixture of carboxylic acid **11**[6] (121 mg, 0.20 mmol), HOBt (134 mg, 0.99 mmol), and diisopropylethylamine (79 μL, 0.46 mmol) in DMF (20 mL) at room temperature. The resulting mixture was cooled to 0 °C whereafter EDC (147 mg, 0.77 mmol) was added. The temperature of the reaction mixture was allowed to reach room temperature and was then stirred for 24 h. The mixture was worked up as follows: removal of the solvent at reduced pressure, dissolution of the residue in EtOAc, washing of the ethyl acetate solution sequentially with water, aqueous saturated $NaHCO_3$, water, and brine, followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The crude product (230 mg) was column chromatographed (SiO_2, $CHCl_3$:MeOH:AcOH 120:2:0.5) to give pure compound **12** (152 mg, 76%, $R_f = 0.22$) as a yellow oil: $[\alpha]^{21}$ +19 (*c* 0.15, $CHCl_3$); IR (neat) $\bar{\nu}_{max}$ 3320, 2975, 1698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.048 (s, 9H), 0.98 (t, $J = 8.8$ Hz, 2H), 1.43 (s, 18H), 2.74−2.84 (m, 8H), 3.67 (s, 3H), 3.71 (s, 3H), 3.85−4.22 (m, 19H), 4.40 (br s, 1H), 4.59 (br s, 1H), 4.63 (br m, 1H), 4.98 (br s, 2H), 5.10 (s, 2H), 5.25 (d, $J = 8$ Hz, 1H), 6.30 (br s, 1H), 7.36 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.10, 28.7, 28.8, 52.6, 52.7, 53.7, 54.98, 55.3, 64.0, 69.3, 69.4, 69.5, 69.5, 69.8, 69.9, 70.0, 70.2, 70.3, 82.3, 82.5, 82.9, 83.3, 128.5, 128.6, 128.9, 155−156 (br), 171.0, 171.8, 172.3; HRMS (FAB^+) *m/z* calcd for $C_{57}H_{76}Fe_2N_4O_{13}Si$ 1164.3877, found 1164.3875.

1-{{(*S*)-2-{(*S*)-2-{(*S*)-1′-[[2-(*tert*-Butoxycarbonyl)amino]-2-[((2-trimethylsilyl)ethoxycarbonyl)ethyl]]-ferrocenyl}-(methoxycarbonyl)ethyl}aminoacyl}-2-(*tert*-butoxycarbonyl)aminoethyl}-1′-{{(*S*)-2-{(*S*)-2-{(*S*)-1′-[[2-(benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]-ferrocenyl}-(*tert*-butoxycarbonyl)ethyl}aminoacyl}-2-(methoxycarbonyl)ethyl}ferrocene (13). A solution of **10** (56.3 mg, 0.09 mmol) in DMF (1 mL) was added to a mixture of carboxylic acid **12** (102 mg, 1.02 mmol), HOBt (38 mg, 0.28 mmol), and diisopropylethylamine (16 μL, 0.09 mmol) in DMF (4 mL) at room temperature. The resulting mixture was cooled to 0 °C whereafter EDC (34 mg, 0.18 mmol) was added. The temperature of the reaction mixture was allowed to reach room temperature and was then stirred for 24 h. The mixture was worked up as follows: removal of the solvent at reduced pressure, dissolution of the residue in EtOAc, washing of the ethyl acetate solution sequentially with water, aqueous saturated $NaHCO_3$, water, and brine, followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue was column chromatographed (SiO_2, $CHCl_3$:MeOH 120:2) to give pure compound **13** (81 mg, 55%, $R_f = 0.31$) as a yellow oil: $[\alpha]^{21}$ +24 (*c* 0.25, $CHCl_3$); IR (neat) $\bar{\nu}_{max}$ 3325.5, 2977.4, 1716.5 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.042 (s, 9H), 0.98 (t, $J = 8.6$ Hz, 2H), 1.42 (s, 27H), 2.71−2.88 (m, 12H), 3.67 (s, 3H), 3.70 (s, 6H), 3.89−4.01 (m, 27 H), 4.09−4.20 (m, 3H), 4.30 (br s, 1H), 4.47 (br s, 1H), 4.58 (m, 2H), 4.98 (m, 3H), 5.09 (s, 2H), 5.30 (br m, 1H), 6.32(br s, 2H), 7.33−7.34 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ −1.10, 28.7, 52.6, 52.6, 53.7, 55.3, 60.7, 64.0, 67.3, 69.3, 69.4, 69.5, 69.5, 69.8, 69.84, 69.9, 70.0, 70.1, 70.2, 80.0, 81.0 82.5, 82.9, 83.4, 128.5, 128.5, 128.9, 155.0, 156.0, 171.1, 171.8, 172.2, 172.3; HRMS (FAB^+) *m/z* calcd for $C_{79}H_{104}Fe_3N_6O_{18}Si$ 1620.5240, found 1620.5243.

1-{{(*S*)-2-{(*S*)-2-{(*S*)-1′-[[2-(*tert*-Butoxycarbonyl)amino]-2-(carboxyethyl)]ferrocenyl}-(methoxycarbonyl)-ethyl}aminoacyl}-2-(*tert*-butoxycarbonyl)aminoethyl}-1′-{{(*S*)-2-{(*S*)-2-{(*S*)-1′-[[2-(benzyloxycarbonyl)amino]-2-(methoxycarbonyl)ethyl]ferrocenyl}-(*tert*-butoxycarbonyl)ethyl}aminoacyl}-2-(methoxycarbonyl)ethyl}-ferrocene (14). A solution of TBAF·$3H_2O$ (27.4 mg, 86.8 μmol) in THF (0.4 mL) was added to a mixture of **12** (81 mg, 55.7 μmol) in THF (2 mL) at 0 °C. The reaction mixture was stirred at room temperature for 24 h and then the solvent was removed at reduced pressure and worked up as follows: dissolution of the residue in EtOAc, washing of the EtOAc phase sequentially with 0.5 M HCl and water, followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue was column chromatographed (SiO_2, $CHCl_3$:MeOH 20:2) to give pure carboxylic acid **14** (33 mg, 44%, $R_f = 0.45$) as a yellow oil: $[\alpha]^{21}$ +24 (*c* 0.250, $CHCl_3$); IR (neat) $\bar{\nu}_{max}$ 3419.6, 2978.9, 1709.8 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.44 (s, 27 H), 2.44 (m, 12 H), 3.69 (d, 9 H), 3.93−4.06 (m, 26 H), 4.30−4.56 (m, 2H), 4.63 (br s, 2H), 5.04 (d, $J = 7.9$ Hz, 1H), 5.12 (br m, 4H), 5.35 (br s, 1H), 6.53 (br s, 2H), 7.35 (s, 5H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 28.3, 32.4, 32.7, 52.3, 53.4, 54.3, 54.9, 55.7, 66.9, 68.8, 69.1, 69.5, 69.7, 69.8, 70.1, 79.8, 80.2, 82.1, 82.9, 128.0, 128.1, 128.5, 136.2, 155.3, 155.6, 170.8, 171.1, 171.4, 172.0, 174.2; HRMS (FAB^+) *m/z* calcd for $C_{74}H_{92}Fe_3N_6O_{18}$ 1520.4516, found 1520.4513.

(2*S*,5*S*,8*S*,11*S*,14*S*,17*S*)-2,8,14-[Methoxycarbonyl]-3,9,-15-aza-4,10,16-oxo-5,11,17-[(*tert*-butylcarbonyl)amino]-[6.6.6](1,1′)ferrocenophane (4). Pd/C (5%, 119 mg) was carefully added (**Warning!** Fire hazard) to a solution of **14** (33 mg, 21.7 μmol) in MeOH (25 mL). The mixture was stirred under 1 atm of H_2(g) for 24 h at room temperature. The catalyst was then removed by filtration through Celite and the filtrate was then concentrated to give amine derivative (22 mg, 74%) as a yellow syrup, which was used directly in the next step. A solution of the amine derivative (20 mg, 14.5 μmol) in DMF (5 mL) was added by a syringe pump (with pump rate 3.3 mL/h) to a stirred solution of PyAOP (43 mg, 29.8 μmol) and DIEA (8.73 μL, 51 μmol) in DMF (15 mL) over a period of 2 h at room temperature under Ar(g). The reaction mixture was stirred at room temperature for 24 h and then concentrated under reduced pressure. The residue was dissolved in EtOAc and worked up as follows: washing of the organic phase sequentially with water, 5% $KHSO_4$, water, and brine followed by drying (Na_2SO_4) and removal of the solvent under reduced pressure. The residue (14 mg) was column chromatographed (SiO_2, $CHCl_3$:MeOH:AcOH 120:2:0.5) to give **4** (8.05 mg, 41%, $R_f = 0.27$) as a yellow viscous mass. Data were identical with those described above.

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Supporting Information Available: MS and HPLC data for the cyclooligomerization step and a table of NOSEY couplings for **3** and **4**, respectively. This material is available free of charge via the Internet at http://pubs.acs.org.

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